A Dissertation on

A CORRELATIVE STUDY BETWEEN SERUM URIC ACID LEVEL AND COMPONENTS OF METABOLIC SYNDROME

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With partial fulfilment of the regulations

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I solemnly declare that this dissertation titled "**A CORRELATIVE STUDY BETWEEN SERUM URIC ACID LEVEL AND COMPONENTS OF METABOLIC SYNDROME**" was done by me from July 2016 to June 2017**,** at Coimbatore Medical College and Government Hospital under the guidance and supervision of **Prof. Dr. K. SWAMINATHAN, M.D.,**

This dissertation is submitted to the Tamilnadu Dr. M.G.R. Medical University, Chennai – 600 032, towards the partial fulfilment of requirement for the award of M.D. Degree in General Medicine (Branch – 1).

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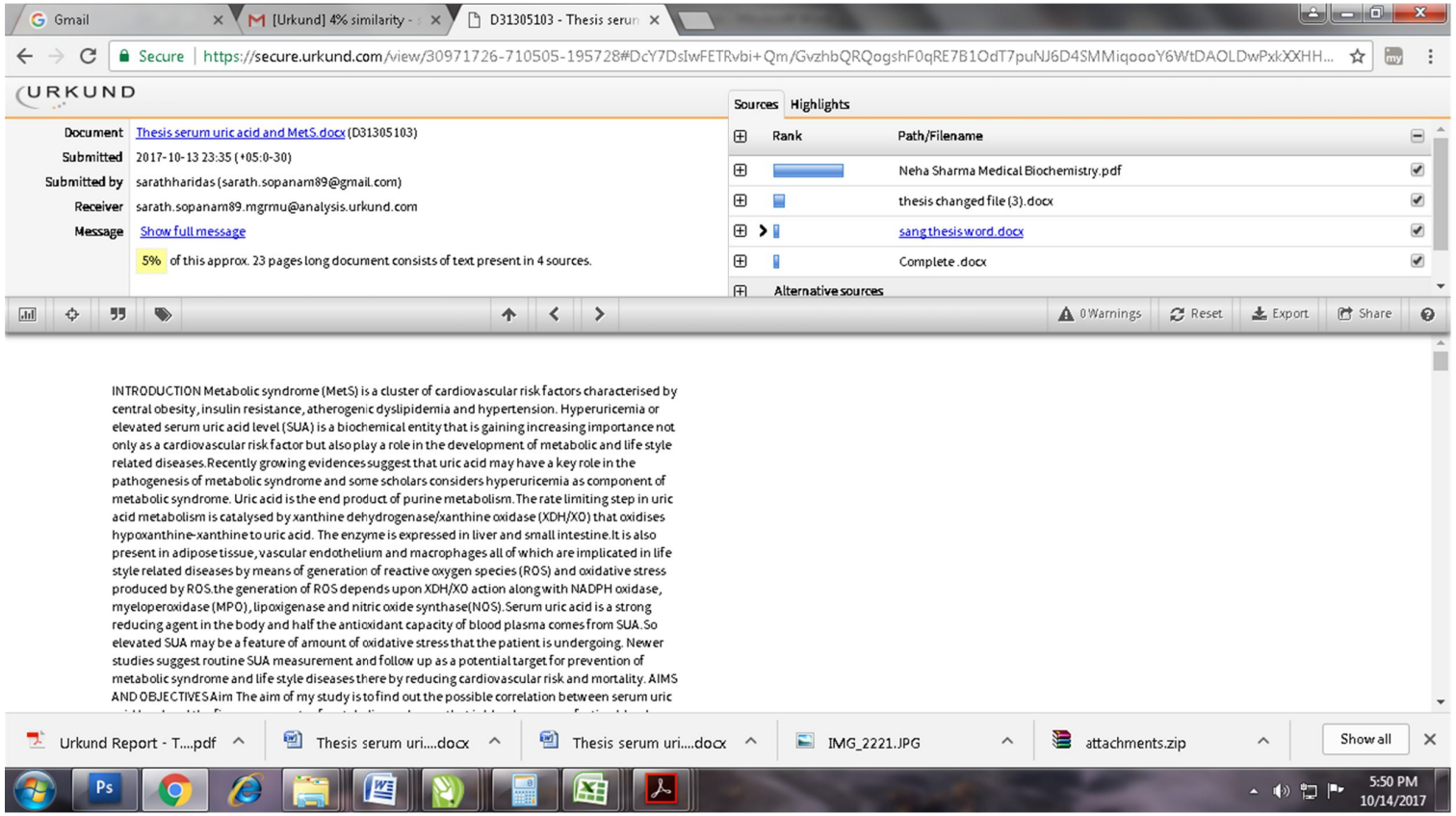
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INTRODUCTION Metabolic syndrome (MetS) is a cluster of cardiovascular risk factors characterised by central obesity, insulin resistance, atherogenic dyslipidemia and hypertension. Hyperuricemia or elevated serum uric acid level (SUA) is a biochemical entity that is gaining increasing importance not only as a cardiovascular risk factor but also play a role in the development of metabolic and life style related diseases.Recently growing evidences suggest that uric acid may have a key role in the pathogenesis of metabolic syndrome and some scholars considers hyperuricemia as component of metabolic syndrome. Uric acid is the end product of purine metabolism.The rate limiting step in uric acid metabolism is catalysed by xanthine dehydrogenase/xanthine oxidase (XDH/XO) that oxidises hypoxanthine-xanthine to uric acid. The enzyme is expressed in liver and small intestine.It is also present in adipose tissue, vascular endothelium and macrophages all of which are implicated in life style related diseases by means of generation of reactive oxygen species (ROS) and oxidative stress produced by ROS.the generation of ROS depends upon XDH/XO action alongwith NADPH oxidase, myeloperoxidase (MPO), lipoxigenase and nitric oxide synthase(NOS).Serum uric acid is a strong reducing agent in the body and half the antioxidant capacity of blood plasma comes from SUA.So elevated SUA may be a feature of amount of oxidative stress that the patient is undergoing. Newer studies suggest routine SUA measurement and follow up as a potential target for prevention of metabolic syndrome and life style diseases there by reducing cardiovascular risk and mortality. AIMS AND OBJECTIVES Aim The aim of my study is to find out the possible correlation between serum uric
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IST OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF CHARTS

ABBREVIATIONS

MetS	Metabolic Syndrome
SUA	Serum Uric Acid
XDH	Xanthine Dehydrogenase
XO	Xanthine Oxidase
ROS	Reactive Oxygen Species
MPO	Myelo Peroxidase
eNOS	Endothelial Nitric Oxide Synthase
HDL	High Density Lipo-proteine
VLDL	Very Low Density Lipoprotein
LDL	Low Density Lipoprotein
W.C	Waist Circumference
eGFR	Estimated Glomerular Filtration Rate
FBS	Fasting Blood Sugar
PPBS	Post Prandial Blood Sugar
CRP	C-Reactive Protein
CAD	Coronary Artery Disease

INTRODUCTION

Metabolic syndrome (MetS) is a cluster of cardiovascular risk factors characterised by central obesity, insulin resistance, atherogenic dyslipidemia and hypertension. Hyperuricemia or elevated serum uric acid level (SUA) is a biochemical entity that is gaining increasing importance not only as a cardiovascular risk factor but also play a role in the development of metabolic and life style related diseases. Recently growing evidences suggest that uric acid may have a key role in the pathogenesis of metabolic syndrome and some scholars considers hyperuricemia as component of metabolic syndrome. Uric acid is the end product of purine metabolism. The rate limiting step in uric acid metabolism is catalysed by xanthine dehydrogenase/xanthine oxidase (XDH/XO) that oxidises hypoxanthine-xanthine to uric acid. The enzyme is expressed in liver and small intestine.It is also present in adipose tissue, vascular endothelium and macrophages all of which are implicated in life style related diseases by means of generation of reactive oxygen species (ROS) and oxidative stress produced by ROS. The generation of ROS depends upon XDH/XO action along with NADPH oxidase, myeloperoxidase (MPO), lipoxigenase and nitric oxide synthase (NOS). Serum uric acid is a strong reducing agent in the body and half the antioxidant capacity of blood plasma comes from SUA. So elevated SUA

may be a feature of amount of oxidative stress that the patient is undergoing. Newer studies suggest routine SUA measurement and follow up as a potential target for prevention of metabolic syndrome and life style diseases there by reducing cardiovascular risk and mortality.

AIMS AND OBJECTIVES

Aim

The aim of my study is to find out the possible correlation between serum uric acid level and the five components of metabolic syndrome, that is blood pressure, fasting blood sugar, fasting triglyceride level,HDL cholesterol level, waist circumference. My study also aims at finding possible correlation of serum uric acid with body mass index.

Objectives

1. To identify the possible correlation between serum uric acid level and the components of metabolic syndrome.
2. To identify the prevalence of hyperuricemia in metabolic syndrome.
3. To identify the possible cut off value for serum uric acid above which the risk of metabolic syndrome is high.

REVIEW OF LITERATURE

Metabolic syndrome

A Swedish physician Kylin was the first to describe about metabolic syndrome in the year 1920, later Reaven described Syndrome X (Insulin resistance, hyperglycemia, hypertension, low HDL cholesterol and raised VLDL Triglycerides) in 1988. At the current era, modern man is facing challenges regarding Metabolic Syndrome and it is well known in creating health related problems (17)

Obesity, the component omitted by Reaven when he first described Syndrome X now has gained its importance in the current scenario, especially visceral obesity. Later a list of names were proposed, yet metabolic syndrome gained its popularity. Metabolic syndrome was attempted to be defined by WHO, European group for the study of Insulin resistance (EGIR) and the National Cholestrol Education Programme – the third adult treatment panel (NCEP – ATP III) Studies were conducted thereafter to ascertain the health related risks in metabolic syndrome. In a study conducted by Framingham, it was found that metabolic syndrome has increased chances of acquiring diabetes mellitus in men five times and in women more than six times (18). WHO and EGIR has a glucocentric definition, while the NCEP – ATP III

definition is mainly focussed on the cardiovascular status, and has proved it efficiency in predicting the cardiovascular risk. Suspiciously low prevalence states in Asian population (20) has brought about changes in NCEP – ATP III definitions for cut off values for obesity ie; waist circumference >/= 90 cm in males and >/= 80 cm in females (21).

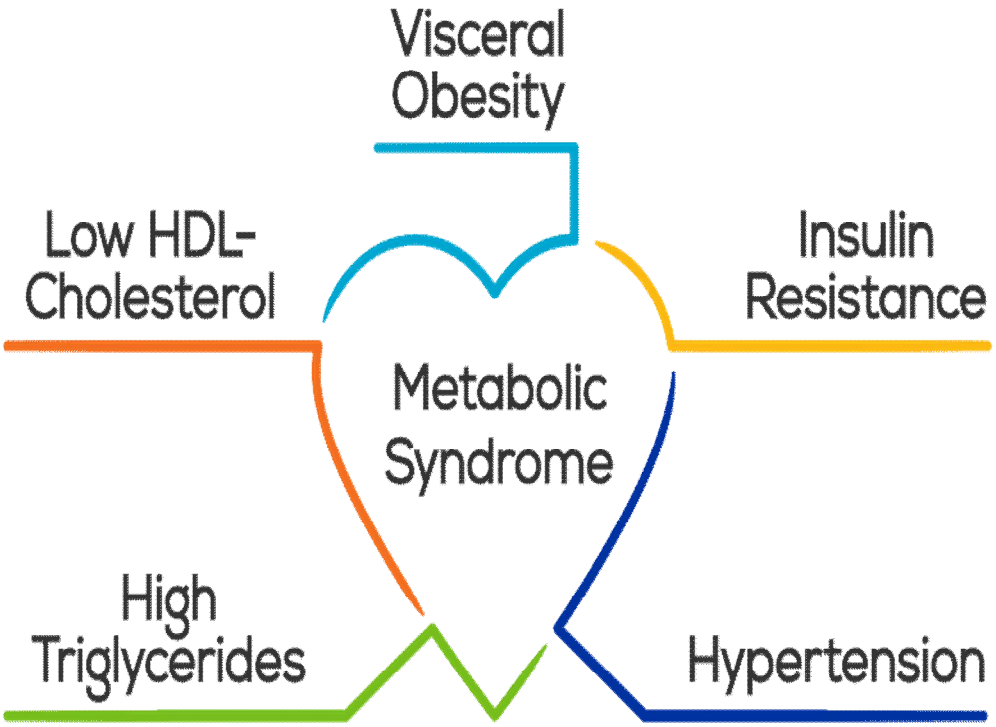

Fig.1 Metabolic syndrome

RISK	DEFINING LEVEL
Abdominal obesity	
Men (waist circumference)	>90 cm
Women (waist circumference)	>80 cm
Triglyceride levels	>150 mg/dL
HDL cholesterol level	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	>/=130/85 mmHg
Fasting plasma glucose	>100 mg/dL

Table.1 NCEP-ATP III criteria for metabolic syndrome(19)

According to new IDF definition diagnosis of metabolic syndrome is made in following manner; central obesity ie; defined as having waist circumference 94cm for European men and 80 cm for European women (ethnic specific values are present for other groups) along with presence of two out of four following factors.

1. Raised TG levels > 150 mg/dL (1.7mmol/L), or specific treatment for this lipid abnormality

2. Reduced HDL cholesterol <40mg/dL (1.03mmol/L) in males and <50 mg/Dl (1.29 mmol/L) in females, or specific treatment for this lipid abnormality.

3. Raised blood pressure: systolic BP > 130 or diastolic BP > 85mm of Hg or treatment of previously diagonosed hypertension

4. Raised fasting plasma glucose > 100 mg/dL (5.6 mmol/L) or previously diagnosed type 2 diabetes mellitus

For values more than 100mg/dL, OGTT is recommended yet not necessary to diagnose metabolic syndrome.

Waist circumference is helpful in determining central obesity and it is ethnic group specific (not in accordance with country of residence). It has been stressed that these values are taken from multiple sources of data and better information is needed to link these to risk factors.

Country /ethnic group	Waist circumference
Europeans	Male 94cm Female 80cm
South Asians	Male 90cm Female 80cm
Chinese	Male 90cm Female 80cm
Japanese	Male 85cm Female 90cm
Ethnic south and Central Americans	Same as South Asians
Sub-Saharan Africans	Use European data
Eastern Mediterraneans and middle east (ARAB)	Use European data

Table.2 IDF data for waist circumference in different ethnicity

*diagnosis is made by presence of three or more risk factors. Indians have a high prevalence of metabolic syndrome considering this fact it is advised to use a cut off value for waist circumference of > 90 cm in males and > 80 cm in females (22).

Role of insulin resistance in metabolic syndrome

Insulin resistance has described the pathophysiology of metabolic syndrome and has become the most recommended hypothesis among the

scientific community .In individuals vulnerable for developing insulin resistance due to genetic predisposition major contributor is stated to be high circulating fatty acids. The sources of being different like the albumin bound fatty acids are derived from adipose tissue; triglycerides stores released from action of hormone sensitive lipase a CAMP dependent enzyme and by action of lipoprotein lipase action on the tissue rich in triglyceride lipoproteins(23). Insulin hormone has an anti lipolytic action on adipose tissue and it has its proven role in the stimulation of lipoprotein lipase. When the action of insulin is interrupted the fatty acid levels are elevated as there is uninhibited lipolysis in adipose tissue. The excess fatty acids also develop insulin resistance in the insulin sensitive tissue by both mechanisms ie; added availability of substrate and modification of the downstream signalling.

Obesity and waist circumference

The concept of obesity has given a different prospect to definition of metabolic syndrome, it prevalence as an epidemic worldwide has brought to light the importance of this factor. Henry resinek and et al says there is substantial cerebral impairement in persons with obesity and metabolic syndrome(20). It has been found that people with obesity and metabolic syndrome are prone to develop cerebral atrophy that leads to cerebral dysfunction. Management of obesity is essential component of

reducing cardiovascular and cerebrovascular mortality. Even though there are pharmacological methods, active exercising and diet modifications are utmost important. Bariatric surgery is used as a last resort.

It has been found that patients with normal nourishment can also develop insulin resistance (24). The distinction between the development of insulin resistance in large waist circumferences and high visceral fat is under debate. Although computed tomography and magnetic resonance imaging can prove it (25). The increased visceral fat levels has direct effect on the hepatic metabolism rather that the effect produced by the increased abdominal subcutaneous tissue which has predominant effect on the systemic circulation. The direct effect on liver results in derangement of glucose and lipid metabolism and would increase the release of prothrombotic factors (26). Though it shows wide difference in pathophysiology visceral fat is predominantly seen in Asians and Indians, while increased abdominal fat is seen in the Americans and Africans (28).

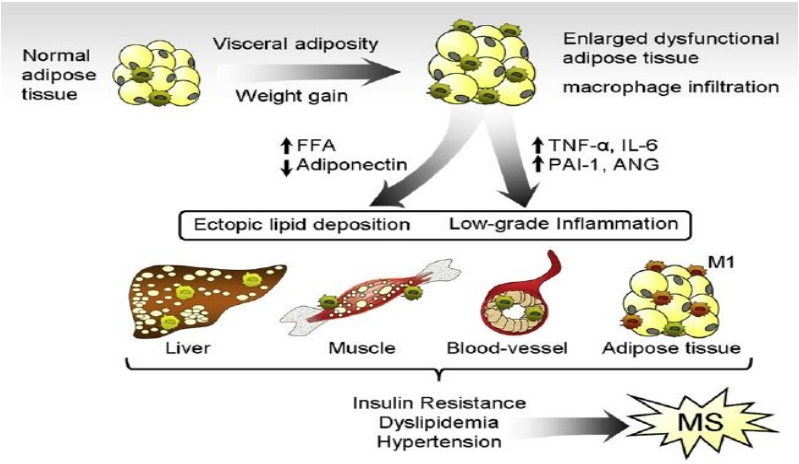

Fig.2 visceral obesity and metabolic syndrome

Dyslipidemia

Increased free fatty acid levels in the liver tends to increase the VLDL levels. The insulin hormone has a complex action on this. Increased fatty acid levels in liver, increase the triglyceride levels and the insulin resistance causes a reduced action of lipoprotein lipase in peripheral tissues. Contribution of altered activity of lipoprotein lipase action to elevated triglyceride level is much less. Hypertriglyceridemia has a significant role in diagnosis of insulin resistance and metabolic syndrome. On the other side a reduction in the HDL levels can lead to metabolic syndrome, which is due to changes in HDL composition and metabolism. Elevated triglyceride levels tend to alter the lipoprotein core composition and results in immediate clearance of HDL from circulation, as cholesterol ester content is decreased (29). Likewise there occurs alteration in LDL composition, where there occurs relative depletion of nonesterified cholesterol, esterified cholesterol and phospholipid with either no change or an increase in LDL triglyceride (30). Individuals with fasting triglycerides more than 2mmol/L is considered to have predominance of small dense LDL.

It is stated that small dense LDL can be more atherogenic due to increased toxicity to endothelial lining,increased ability to transit between

endothelial basement membrane,increased adhering capacity to glycosaminoglycan and increased susceptibility to oxidation.

Glucose intolerance

The defect in action of insulin is mainly in the inability to supress the glucose production by liver and kidney and to mediate the glucose uptake and metabolism in peripheral tissues. Fatty acid mediated modification in pancreatic beta cells lead to inhibition in glucose level dependent release of the hormone. Although free fatty acids can stimulate insulin secretion prolonged exposure finally lead to resistance (31). The resistance developed due to prolonged exposure of fatty acids is by means of different mechanisms resulting in lipotoxicity (32). Chances of developin diabetes in prone person is higher when exposed to an environment of insulin resistance.

Diabetes

Bjornstord et al says the relationship between serum uric acid and diabetes is well established, but an inverse relationship is observed in patiets with type 1 diabetes. This is because of low levels of serum uric acid levels in patients with type 1 diabets.

Diabetes is the syndrome characterised by disturbances in hyperglycemia, derangements in fat and protein metabolism with deficiencies in insulin secretion that could be absolute or relative.

History of diabetes carries us back to the ages where Egyptians described the disease with passage of high amount of urine in early 1550 B.C.

A renowned Greek physician later named disease as DIABETES meaning ‘to run through’ or ‘siphon’. Later it was described, to be disease with characteristics like sweet urine and polyuria hence, a new name came into existence ‘diabetes mellitus’. In the coming centuries, certain pancreatic cells responsible for insulin secretion was found; the deficiency of which led to the disease described above. The sweetness of urine was due to the presence of sugar. Recombinant DNA was later discovered and now the scenario has advanced to those stages, where as a part of treatment of diabetes, the transplantation of pancreas and islet cells are successfully been practiced.

Newer classification of DIABETES:

1) PRIMARY

TYPE 1(auto immune)

Immune mediated

Idiopathic

TYPE II (Non – autoimmune)

OTHER TYPES

- Genetic defects of beta cell function (MODY 1,2,3,4,5)
- Genetic defects of insulin secretion

2) SECONDARY

- Pancreatic diseases
- Hormonal abnormalities
- Insulin receptor antibodies
- Drugs and chemical induced
- Associated with genetic syndromes
- Gestational diabetes mellitus

Etiology of type 2 diabetes

Mainly two physiological processes are associated with the development of type 2 diabetes. First, the abnormality in insulin secretion and second the resistance to the action of the hormone at the target tissues. Most of the affected individuals are obese and earlier it was believed to be obesity induced secretory defect. In the later studies it was established that, obesity never lead to diabetes in the presence of normal

beta cell function. The relative insulin deficiency may cause an increase in the alpha: beta cell ratio and relative excess glucagon is characteristic to type 2 DM.

Role of insulin resistance:

The insulin biological response is reduced to 40% in type 2 diabetes. Effects of insulin resistance has its effect on the glucose metabolism in liver and peripheral glucose output. Although the confirmed reports on the mechanism of insulin resistance is not yet known, but postulates say that it is due to the reduction in the receptors on the target tissues that lead to the condition. Earlier the FBS, PPBS and estimation of glucose levels in urine was used, but the major drawbacks in the tests made the estimation of glycemic status to be determined by the glycosylated haemoglobin values. It gives a more wide view about the glycemic status of the individuals.

	Venous blood glucose	**Venous blood glucose**	**Capillary blood glucose**
FBS	**>140**	**>120**	**>120**
RBS	**>200**	**>180**	**>200**

Table.3 WHO criteria in the diagnosis of Diabetes

American diabetes association recommendations

As per the International expert committeeworking under the sponsorship of ADA, established in May 1995.

1) Symptoms of diabetes plus random blood glucose concentration >/= 200 mg/dl. Random means any time of the day without regard to time since the last meal.

2) Fasting blood sugar > 126mg/dl. Fasting means no caloric intake for atleast 8 hrs.

3) 2 hr plasma glucose >200 mg/dl during an oral glucose tolerance test, which is performed, as described by WHO with a glucose load containing equivalent of 75g of anhydrous glucose dissolved in water. If any of the three is positive, it has to be confirmed with any one of the three tests on subsequent day.

Hypertension

The relationship between hyperuricemia and Hypertension is well established entity. Many mechanisms have been proposed for the development of hypertension in hyperuricemia. Induction of oxidative stress, activation of renin angiotensin aldosterone system and inhibition of nitric oxide are the most accepted mechanisms. The final common

pathway of all the mechanisms is the development of renovascular disease causing by infiltration of the renal arterioles by T-cells and macrophages causing occvlusion. The intracellular uric acid, rather than the extracellular uric acid plays major role in the pathological mechanisms that leads tpo hypertension.Type 2 diabetes mellitus patients have higher intracellular uric acid when compared to type 1 diabetes mellitus patients, which explains the paradoxical effect of type 1 diabetes on serum uric acid and development of hyprtension.positive effect of hyperuricemia on blood pressure I type 1 diabetes occurs more commonly I patients with a creatinine clearance of less than 60mL/min/1.73m2. The results of two large meta-analysis showed for every 1mg/dL increase in serum uric acid levels there is a 12% to 15% increase in hypertension. Many scholars consider hyperuricemia as an independent risk factor for hypertension. Some of the south Asian studies showed significant relationships between hyperuricemia and hypertensive retinopathy, which clearly shows the significance of hyperuricemia in chronic hypertension. Certain studies revealed 6% increase in hypertensive retionopathy with each milligram elevation in serumuric acid levels.Sandra N ofori et al says the incidence of target organ damage due to hypertension increases substantially high with hyper uricemia. Which also shows the positive correlation of serum uric acid level with huypertension.She also says that countries where limited facilities to

diagnose early target organ damage, serum uric acid level can be a useful predictor.which can be used as an inexpensive and effective screening test. Delay in detecting hypertension also leads to significant target organ damage and hence hyperuricemia can be used as an effective way to detect people who needs further evaluation with expensive procedures or tests. Early identification of people with target organ damage is the most important thing to prevent mortality due to complications.

There is well known relationship between insulin resistance and hypertension (33) and is stated by multiple pathophysiological mechanisms. Insulin has a vasodilatory effect (34) and effects on kidney in matter of sodium reabsorption (35), which is lost in state of insulin resistance (36). Although the effect on the kidney is preserved (37) under such circumstances. Insulin also increases the activity of sympathetic nervous system (38), which is preserved in insulin resistance state. Insulin resistance has only a little contribution to development of hypertension in metabolic syndrome (39). Insulin resistance also shows an array of other manifestation which is excluded from diagnostic criteria.

Panel: changes with insulin resistance (40)

LIPOPROTEINS

1. Increased Apo-B
2. Decresed Apo A-1
3. Small dense LDL and HDL
4. Increased Apo C-3

PROTHROMBOTIC

1. Increased fibrinogen
2. Increased plasminogen activator inhibitor 1
3. Increased viscosity
4. Increased uric acid levels

INFLMMATORY MARKERS

1. Increased WBC count
2. Increased interleukin 6
3. Increased TNF α
4. Increased CRP

VASCULAR

1. Microalbuminuria

2. Increased asymmetric dimethyl arginine

OTHERS

1. Fatty liver

2. Polycystic ovarian disease

Uric acid

Uric acid is the breakdown product of purine metabolism. It is a weak acid with pKa 5.75 and 10.3 . Due to the presence of urea, proteins and mucopolysaccharides it is more soluble in urine than that in water.

History

Swedish chemist Scheele isolated uric acid from urinary tract calculus in the year 1776 (41), later Wollaston isolated the same from the tophus removed from his ear in 1797 (42). After more than 50 years from early observations, a British physician Alred Barry Garrod chemically isolated the material from the urine blood of gouty patient (43). His observations established a relationship between gout and hyperuricemia.

However Garrod's concept was later rejected when Folin proposed a reliable method to determine the uric acid levels (45).

Structure and chemistry

Fischer established the chemical nature of uric acid to be 2,6,8 trioxypurine (46). Disruption of purine ring with removal of carbon -6 as carbon dioxide and formation of allantoin and other products when treated in neutral alkaline solution. When it oxidised in the acidic medium, alloxan is the product and when treated with ammonia, a purplish red substance is obtained called ammonium purpurate (murexide test- colorimetric test to determine the presence of uric acid based on its reducing properties).

Synthesis

Although purine nucleotides are synthesised and degraded in all tissues, while urate is produced I those tissues containing xanthine oxidase (liver, small intestine). It can be synthesised by endogenous protein degradation and by means of denovo synthesis; where the latter contributes more to the production. Daily purine intake has its influence in urate metabolism.

The release of the nucleic acid causes the release of the proteases that degrade the nucleoproteins. Poly nucleotides are depolymerised

under its action and split to nucleotides by nucleases. Nucleotides under the action of nucleotidases gives purines, pyrimidines and phosphoric acid. The dietry purines are excreted as uric acid, whereas the pyrimidines are further degraded by other metabolic pathways. There are three important enzymes involved in urate production.

1. PP ribose-P-amidotransferase(PPRP Amidotransferase)
2. Hypoxanthine Guanine Phospho Ribosyl Transferase
3. Xanthine oxidase

PPRP Amidotransferase is the enzyme catalysing the initial reaction unique to purine biosynthesis. It is the rate limiting enzyme of the pathway which is inhibited by ribonucleosides and promoted by PPRP.

HGPRT is the enzyme which is deficient in Lesch Nyhan syndrome, a salvage enzyme that helps in utilisation of hypoxanthine, converts to inosine that has negative feedback on PPRP amidotransferases. Xanthine oxidase is required in the final steps of uric acid metabolism.

The higher rate of production will result in higher plasma levels of uric acid. Therefore, changes are causing increase in rate of pathway which may be evident in hyperuricemic individuals.

Denovo purine synthesis, is a two- step resulting in purine ring formation. First, PPRP and glutamine combines, being catalysed by amidophosphoribosyl transferase. The enzyme is regulated by enzyme and the purine metabolites that provides the feedback inhibition.

A secondary pathway is the salvage of purine bases by HGPRT. This enzyme catalyses the combination of hypoxanthine and guanine and produce ribonucleotides IMP and GMP. Increased salvage pathway retards the denovo synthesis and reduce the PPRP levels and cause increase in inhibitory ribonucleotides

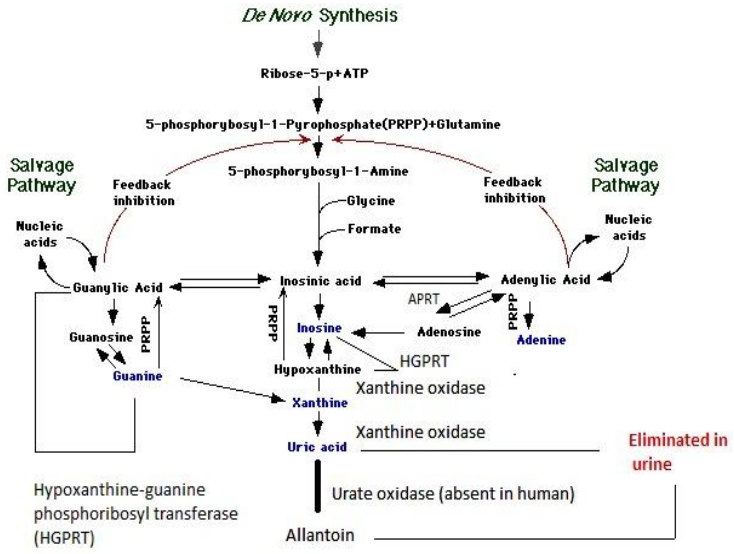

Fig.3 Pathway of urate production

Dietary intake:

Diet provides an important exogenous source of purines. Higher intake of food products containing nucleic acid amy increase the uric acid levels. The contribution by diet is proportionate to the dietary intake. However, a purine free diet may decrease the uric acid levels by 1 mg/dL. Whereas the higher intake of purine rich foods may increase the the uric acid levels to much higher concentrations. Thus food rich in purine has a significant role in raising the uric acid levels.

Normal values:

Usually, urate levels in males is about 1200mg and about 700mg is produced daily in body(47). The production is balanced by excretion of 500mg of uric acid by urine and 200mg by small intestine. An imbalance in the above process may alter the normal uric acid levels of the body.

The normal serum values vary with sex and age. Children have uric acid levels of 3-4mg/dL, which rise during puberty to adult levels in males; but in females the levels are low till menopause. This variation is due to the higher rate of excretion in females.

Mean urate levels of men is 5.3mg/dL and females till menopause is 4.7mg/dL. After attaining menopause the values in women approximate to values of men. Variations are also seen in accordance

with the built of the person, metabolic conditions and according to habits; alcohol intake.

Excretion of uric acid:

Out of the total production in the body two third to one third is excreted via renal pathway. The remaining is excreted through small intestine, where intestinal bacteria act on the uric acid and is broken into soluble products. The plasma concentration is the determining factor for the amount excreted via intestine. Decrease or increase in the renal clearance may alter the plasma concentration.

Steele and Riesel Bach(48) proposed the four component model related to renal clearance of uric acid.

1. Glomerular filtration
2. Pre secretory tubular reabsorption
3. Tubular secretion
4. Post secretory reabsorption

Normally, uric acid is totally filtered in the renal glomeruli, later to be reabsorbed by proximal tubules. 5-10% is later secreted into distal tubules and excreted in urine. The 98% of filtered urine is later reabsorbed.

It was discovered that almost all the secreted urine is later reabsorbed (49). Urate filtration vary by the glomerular filtration rate. Tubular reabsorption is an active process closely related to sodium reabsorption. Expansion of ECF increase the urate clearance by inhibition of tubular reabsorption (50). When in a condition where the ECF volume contracts, the urate excretion is at minimal level causing hyperuricemia. The tubular secretion is proportional to plasma uric acid concentration. Normally, kidney excrete 5 – 10% of filtered load of uric acid.

Hyperuricemia

Hyperuricemia is a condition produced by either increased production or reduced excretion of uric acid. Elevated levels of uric acid of more than 7 mg/dL in men and > 6mg/dL in females is stated as hyperuricemia(51). In epidemiological studies, hyperuricemia is mean plus two standard deviation of values ie; determined from randomly selected healthy population. When measured, in unselected individuals, 95% have serum urate concentration <7mg/dL. In relation to risk of disease, >7 mg/dL of uric acid is associated with gouty arthritis.

Causes of hyperuricemia

1. URATE OVERPRODUCTION

- Primary idiopathic
- HGPRT deficiency
- PPRP synthase overactivity
- Hemolytic processes
- Lymphoproliferative diseases
- Meloproliferative diseases
- Polycythemia vera
- Psoriasis
- Rhabdomyolsis
- Paget's disease
- Exercise
- Alcohol
- Obesity
- Purine rich diet
- Glycogen storage diseases (type V and VII)

2. URATE UNDEREXCRETION

- Primary idiopathic
- Renal insufficiency
- Polycystic kidney disease
- Diabetes insipidus
- Hypertension
- Lactic acidosis
- Ketoacidosis
- Hypothyroidism
- Hyperparathyroidism
- Toxaemia of pregnancy
- Lead intoxication
- Bartter's syndrome
- Down syndrome
- Drugs

  Salicylates

  Diuretics

  Alcohol

  Levodopa

  Ethambutol

  Pyrazinamide

  Nicotinamide

3. COMBINED MECHANISMS

- G6PD deficiency
- Alcohol
- Shock
- Fructose 1 phosphate aldolase deficiency
- Physical exercise
- Status epilepticus
- Myocardial infarction

Uric acid marker of cardiovascular disease, metabolic syndrome and type 2 diabetes mellitus:

Controversies exist in stating serum uric acid as risk factor (56,57) while it has already been proved as risk marker in cardiovascular disease and renal disease especially in patients with hypertension , diabetes and heart failure. Serum uric acid (SUA) is a graded marker for determining the risk of developing coronary heart disease (CAD) and cerebrovascular accident (CVA) (56, 58-68). A recently published study by LK Niskanen *et al.* established this fact and related higher uric acid levels and development of CVD in middle aged men (58). In 1951, Gertler MM and White *et al.* found that development of CAD in males below 40 years had direct relation with serum uric acid levels (69).

Later a larger trial in 1967 revealed the initial interest in relation between SUA and CVD, that had 5127 participants' epidemiologic, seminal Framingham study. The paper by Kannel *et al.* noted an elevated SUA was also published same results in age group 30-59 years (70). It

was earlier known that there existed a relation between elevated levels of lipoproteins in development of CAD; now relation between elevated SUA is also established. The authors also noted the incidence of accelerated atherogenesis in the individuals with evidence of impaired purine or carbohydrate metabolism. It is important to know how the high SUA bring about accelerated atherosclerosis. Furthermore the hyperuricemia also predicts the onset of hypertension in the near future (66). Johnson *et al*. demonstrated that hyperuricemia predicts risk of CAD in general population, hypertensive individuals and patients with pre-existing CVD.

There are clustering groups with increased risk of CAD in association with hyperuricemia. In all these the high SUA levels causing risk is explained by different metabolic mechanisms.

A-FLIGHT-U ACRONYM Identification of multiple metabolic toxicities and injurious stimuli responsible for ROS production.

A Angiotensin II

Amylin

Apolipoprotein

Antioxidant reserve compromised

Absence of antioxidant network

Ageing

Asymmetric dimethyl arginine

F Free acid toxicity/ obesity toxicity triad

L Lipotoxicity-Hyperlipidemia/obesity/ toxicity triad

I Insulin toxicity: endogenous hyper insulinemia

G glucose toxicity (sorbitol polyol pathway)

H Hypertension toxicity

Homocysteine toxicity

Hs –CRP

T Triglyceride toxicity

U Uric acid toxicity

Uric acid as an injurious stimuli to blood vessel endothelium :

The upper one third of normal physiological range and abnormal levels of SUA is one of deleterious factor causing injury to the endothelium mainly to the arterial wall and capillary, finally endothelial dysfunction results that lead to remodelling of the blood vessel wall through oxidation reduction stress. Multiple deleterious stimuli is noted in association with atherosclerosis in type2 diabetes and metabolic syndrome. Redox stress activates the nuclear transcription factor; NF kappa B. Overtime, morbidities and mortalities occur by injurious stimuli listed under A-FLIGHT-U acronym. Each of these stimuli is

considered to be individual risk marker in development of CAD and when to act together reaction has synergistic effect. The free radicals modify LDL and retain the molecule in the intima of the blood vessel by oxidative modification. The free radicals like hypochlorus acid, peroxynitrite; selected oxidative enzymes like xanthine oxidase, myeloperoxidase and lipoxygenase are responsible for the modification of LDL. The simple concept that SUA in patients with CVD, MS, T2DM, hypertension and renal disease may reflect a compensatory mechanism to counter oxidative stress; but the individuals with these diseases are generally associated with worse outcomes.

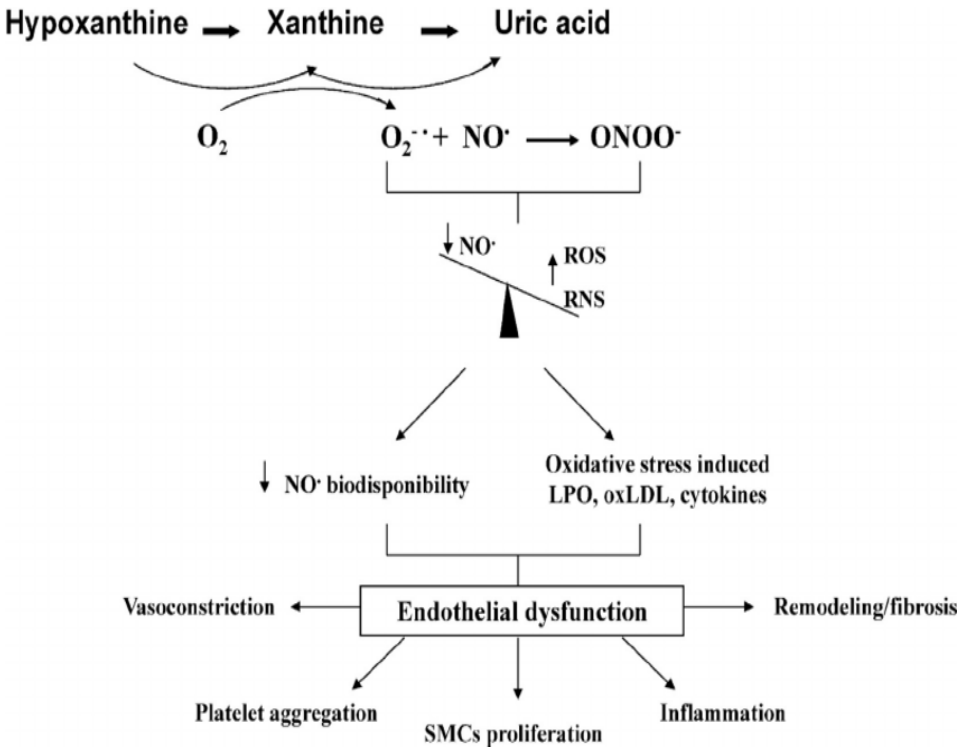

Fig 4. Urate in oxidative stress and endothelial dysfunction

Urate redox shuttle:

Anti-oxidants become pro oxidants in certain situations (71-75). Hence serum uric acid levels in the early stages of atherosclerosis acts as anti-oxidant(73) but when there is elevation in the plasma concentration ie; in upper one third of normal range >4 mg/dL and abnormal values like >6mg/dL in females and >7 mg /dL in males it plays the role of a pro oxidant. Thus an antioxidant – prooxidant shuttle may be seen in human body, at the vascular structures (vessel intima in larger vessels and sub endothelial capillary interstitium in smaller capillaries (71, 72). Thus a paradoxical change occurs in the vascular structures.

The shuttle depends on certain factors mainly the environment, location, pH, the surrounding oxidant media, depletion of other local anti-oxidants, and the concentration of the substrate, the availability of the oxidant substrate and oxidant enzyme. In the process of atherosclerosis the intima has an acidic pH (74), depletion of antioxidants with an underlying increase in oxidant stress and ROS, commonly associated with uncoupling of the eNOS enzyme and reduction in the naturally produced anti-oxidant. This damage occurs in the microvascular structures in hypertensive and diabetic patients in addition to the pathological changes of the disease. Nitric oxide and the vitamin C has inhibitory action against the prooxidant nature of uric acid.

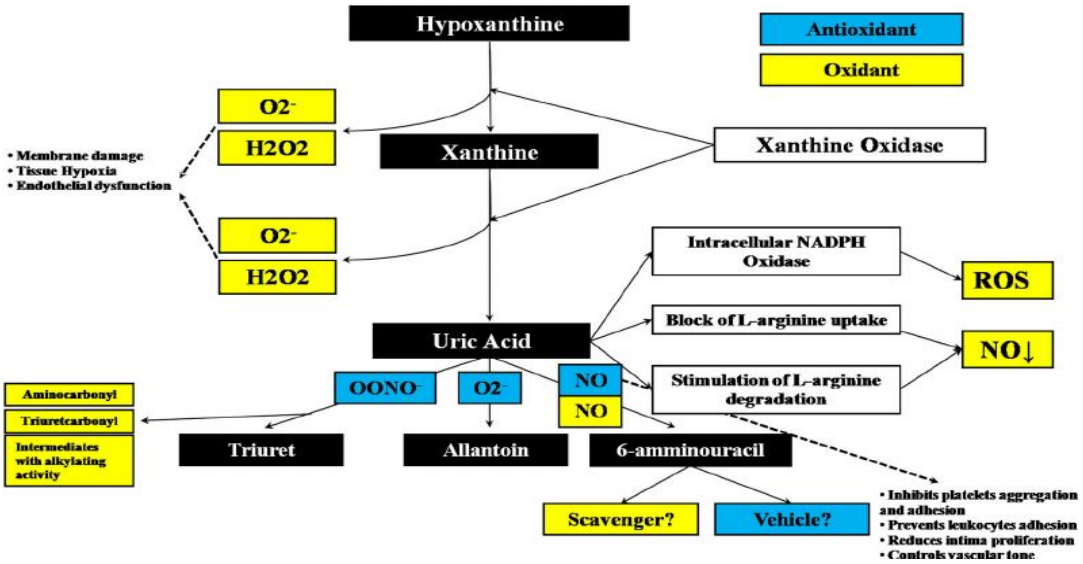

Fig 5. Urate redox shuttle

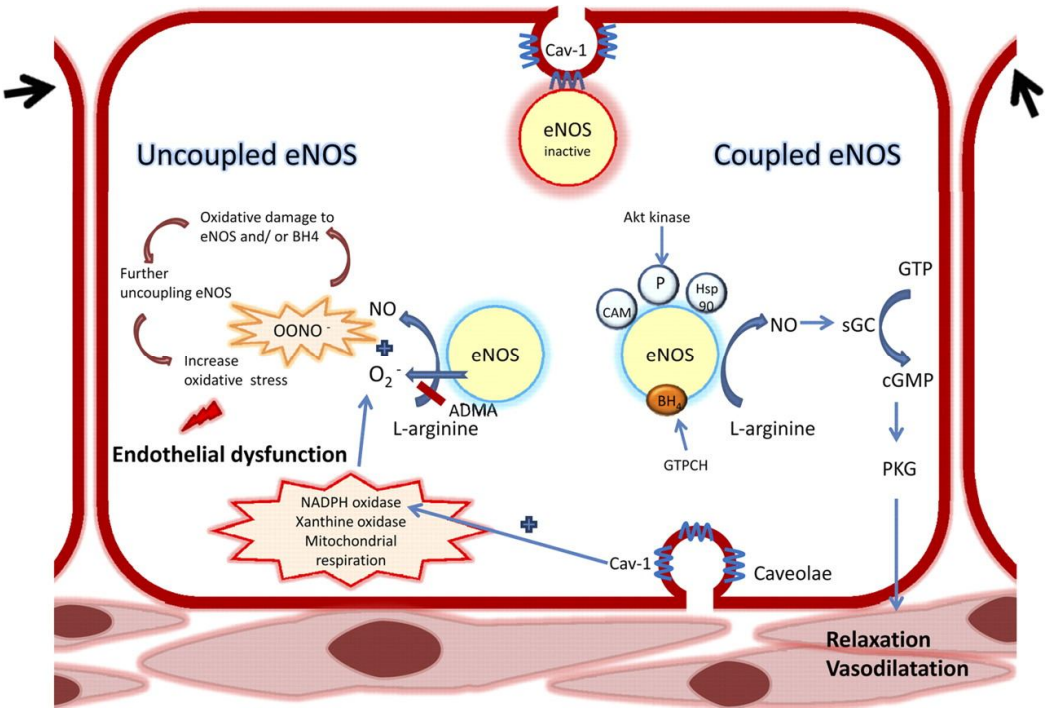

Fig 6.Coupling and un-coupling of eNOS in Endothelial dysfunction)

The ANAi acronym:

ANAi acronym has been developed to stress the effects of SUA in accelerated atherosclerosis plaque; A: APOTOSIS, N: NECROSIS, A: ACIDIC ATHEROSCLEROSIS PLAQUE ANGIOGENESIS, I: INFLAMMATION, INTRAPLAQUE HAEMMORAGE INCREASING THE RBC INCREASING IRON AND COPPER INSIDE THE PLAQUE. This acronym helps us to get a vivid picture about the SUA resulting in the development of antioxidant- prooxidant urate redox shuttle. Reactions that involve the copper and iron have a remarkable role in the oxidative stress in plaques. Fenton and Haber-Weiss reactions of iron and other reactions involving copper are prone to create the oxidative stress.

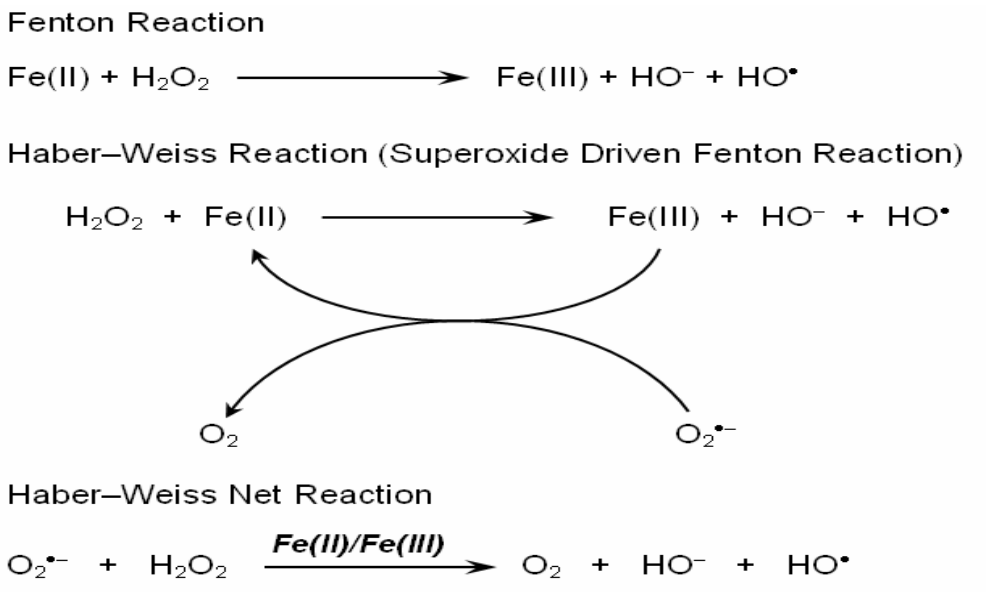

Fig 7. Fenton and Haber-Weiss reactions

The hydroxyl radicals undergo further reactions resulting in the production of ROS. The addition reaction, hydrogen abstraction, electron transfer, and radical interactions are the reaction mechanisms involving the production of the reactive oxygen species. In addition to these the copper can undergo further reactions involving other factors resulting in the production of lipid peroxidases and ROS. The ruptured plaques thus accelerate the atherogenesis and the vulnerability of rupture of other plaques providing a favourable environment by release of iron and copper (76) and also by increased uric acid levels attained by the apoptosis and necrosis of vascular cells and inflammatory cells.

Endothelial function and endothelial nitric oxide (eNo)

The endothelium has the capacity to synthesise and secrete different biologically active factors responsible in regulating inflammation, tone of the vasculature and its growth, lipid metabolism, arterial vessel wall and capillary subendothelial matrix remodelling and finally the modulation of coagulation and fibrinolysis. The enzyme endothelial nitric oxide synthase and its product endothelial nitric oxide has a key role to play in the normal functioning of the vessels. Hence these are considered to act as the maestro. In the absence of the enzyme the endothelium becomes a net producer of free radicals like superoxides and ROS.

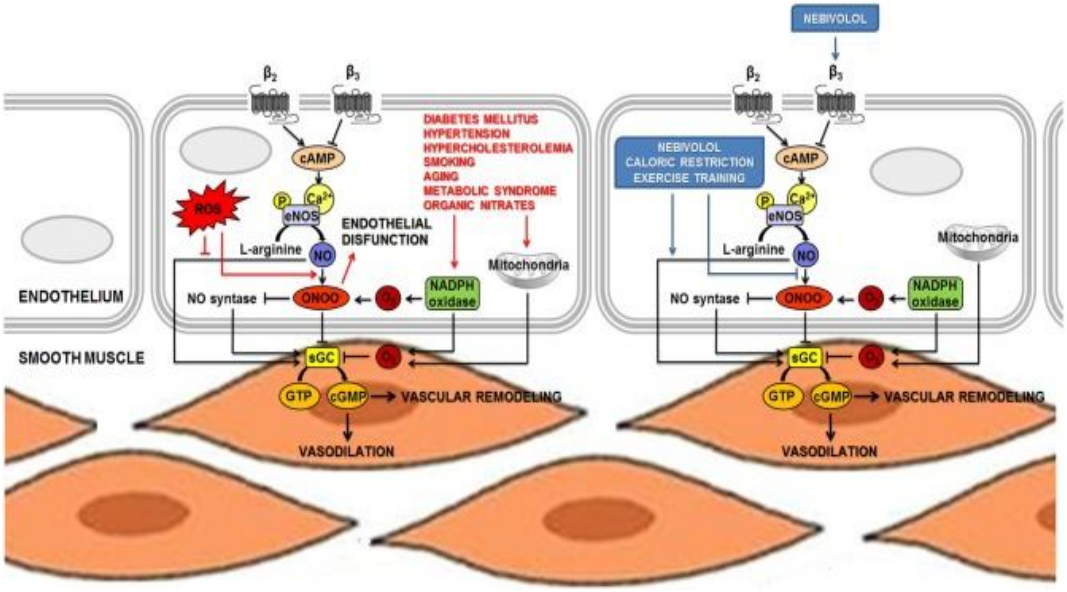

Fig 8. Endothelial dysfunction leading to vascular remodelling

It has been found that there are various factors influencing the uncoupling of the eNOs enzyme; like hyperuricemia, including the antioxidant- proxidant urate shuttle [A-FLIGHT-U toxicity, ROS, T2DM, Pre-diabetes, T1DM, insulin resistance, MS, renin angiotensin aldosterone activation, angiotensin II, hypertension, endothelin, dyslipidemia- hyperlipidemia, homocysteine, and asymmetrical dimethyl arginine (ADMA)] (77-79). Xanthine oxidase –oxidoreductase XO) is immunohistochemically localised within atherosclerotic plaques allowing purine metabolism to happen at the endothelial cell under the proper machinery, where the sites of reaction being the plasma membrane as well as cytoplasm and is capable excessive production of uric acid along the same time generating excessive and detrimental ROS (80).

To summarise: healthy endothelium produced eNO while the dysfunctional endothelium is responsible for the production of superoxide associated with MS, T2DM, and atherosclerosis (77).

Uric acid and inflammation

Uric acid can be substantiated to level of a sensitive marker to detect the vascular inflammation. In most of the situations increased apoptosis and necrosis of the cells in vulnerable plaques causes increased breakdown of the nucleic acid resulting in the excess production of the uric acid. Hence it is not surprising to relate the elevated levels of uric acid and metabolic syndrome. In many of the context the uric acid and the CRP can be included as both the risk marker and risk factor. Due to its presence in the scenario of the atherosclerosis and related complication, it is a proven sensitive marker of vascular inflammation. Uric acid also induces the factors like, nuclear transcription factor (NF- kappa) and monocyte chemoattractant protein -1 (MCP-1). Regarding TNF alpha it has been shown that SUA levels correlate well with the higher levels of this factor in conditions like congestive cardiac failure Olexa P *et.al*. In such circumstances it can be used to assess the severity of the systolic dysfunction and also the progressing inflammatory changes in the patients suffering from congestive cardiac failure.

Uric acid stimulates the human mononuclear cells to produce various interlukeins and tissue factors, including IL-6, IL-1 beta and TNF alpha. It was statistically proven by Tamakoshi *et.al* , in a study conducted in Japanese men of age 34-69 years, that an important correlation do exist between the existence of metabolic syndrome (BMI, total cholesterol, triglycerides, LDL-C, fasting glucose, fasting insulin, uric acid, systolic /diastolic BP) and higher levels of CRP. Meanwhile, HDL-C has a negative correlation with CRP. It was able to conclude from the study that a relation do exist between the elevated CRP and MS at low grade inflammatory states. It should also be kept in mind that CRP levels can be slightly increased in elderly individuals and hence in determining the relation between elevated CRP and SUA, as CRP levels can be seen elevated due to various reasons in old aged due to underlying disease conditions.

Uric acid and chronic renal disease

Hyperuricemia is the ultimate outcome of either the increased production or the decreased excretion of uric acid. Any cause of decreased glomerular filtration, tubular excretion or increased reabsorption result in the higher levels of SUA. The elevated SUA is the predictor of impairment renal function in those individuals who had a normal renal function. In diabetics rising serum uric acid levels suggest

the onset of a condition called overt nephropathy. While, a reduction in SUA levels a hint of later onset nephropathy or reduced progression of disease. An elevated SUA is the important indicator of the disease condition and progression, where it is helpful in determining the global risk associated with the diabetes and overt nephropathy. High serum uric acid levels also contribute to the damage of the endothelium and increase oxidative stress in glomeruli and the tubular interstitium with the associated increased remodelling fibrosis of kidney. In addition to this it also lead to the onset of atherosclerosis and the pro inflammatory state. All these may reduce the vascular supply to the organ reducing the blood flow through afferent arteriole and at the end hinder the excretion of uric acid. The glomeruli may have deleterious effects from the elevated uric acid levels as it endothelial dysfunction caused by oxidative- redox stress result in glomerular remodelling. Changes may happen in the blood vessels due to SUA in hypertensives and the remodelling occur in the glomeruli and the tubule interstitium, causing renal impairment. Increased ischemia- ischemic reperfusion would activate the xanthine oxidase mechanism and contribute to the increased production of ROS. The reaction may result in the generation of H2O2 and oxidative stress that result in remodelling of the renal architecture. Hyperuricemia could increase the urate crystal formation, elevated levels of the uric acid induce the inflammatory and remodelling changes in renal medulla. A

recent publication by Hsu SP *et.al* revealed a J shaped curve association with SUA levels and all-cause mortality in hemodialysis patients. The study demonstrated, a decreased serum albumin in patients with underlying diabetic nephropathy and in patients with SUA in lowest and highest quintiles had higher incidence of mortality. It is surprising to note that in larger trials conducted it was found that the increased SUA and cardiovascular risks showed a J shaped curve regarding mortality incidence and the lower risk occurring in the second quartile.

Johnson RJ *et al.* have speculated that the increased risk of lowest quartile was due to the reduced antioxidant activity, while increased risk at the higher levels reflects the role of uric acid in damaging the vessel walls and effects in hypertensives through the antioxidant and proxidant urate redox shuttle. This would suggest that treatment with xanthine oxidase inhibitors should strive to bring levels to the range of 3-4 mg/dL and suggest not to go lower that the prescribed range.

Uric acid and hypertension

Hypertension has a strong association with hyperuricemia. SUA levels are elevated in hypertensives and hyperuricemia is seen in 25% of untreated hypertensives, 50% of the subjects taking diuretics and 75% of patients with malignant hypertension (81). Various mechanisms exist that associate hypertension with hyperuricemia

1. Decreased renal blood flow (reduced GFR) that enhance renal absorption.

2. Microvascular disease leading to tissue ischemia

3. Ischemia with associated increased lactate production that blocks urate secretion in proximal tubule and increased uric acid synthesis due to increased RNA-DNA breakdown and increased purine metabolism, that enhance the production of urate and ROS by xanthine oxidase.

4. Ischemia resulting in the increased production of xanthine oxidase leading to high urate levels and ROS.

These associations with enchanced XO production and ischemia may help to understand the reason of higher SUA levels in preeclampsia and congestive heartfailure. The endothelial dysfunction, local oxidant generation, higher levels of circulating cytokines and the proinflammatory states are responsible for the increased vascular stress due to oxidative-redox stress in vascular tissues in patients with CVD and hypertension. Oxidative redox shuttle results in the derangement of the normal antioxidant mechanisms of the endothelium and result in production of the ROS and especially stressing in the production of superoxides that cause uncoupling of the enzyme endothelial nitric oxide

synthase that finally reduce the production of nitric oxide in endothelium. This mechanism can be applied in the patients with diabetes and congestive cardiac failure (66,79). It is fascinating to note that the factors like allopurinol and oxypurinol are capable of reversing the impaired eNO production in both cardiac failure and diabetes (86-88). A study by Lin KC *et al.* was able to demonstrate that the high blood pressure levels were having good predictive value in the incidence CVD in those showing high SUA levels (83). Clinical studies conducted in separate laboratories proved that systemic hypertension developed in the rat specimens with higher uric acid levels, and was under uricase inhibitor administration (84, 85). This hypertension associated with increased renin and the decrease in the neuronal nitric oxide synthase in JG apparatus. ACE inhibitors were used to prevent the so developed hypertension as the relation between renin angiotensin system and the NOS enzyme was revealed by the study. It can also be reduced by the administration of L-arginine.Hypertension and the associated factors involved can be controlled by maintaining the serum uric acid levels in the normal range. It was suggested that the usage of allopurinol and a uricosuric benziodarone was able to maintain the normal uric acid levels. The uric acid levels having a pathogenic role in development of the above diseases was proven by such models (66).

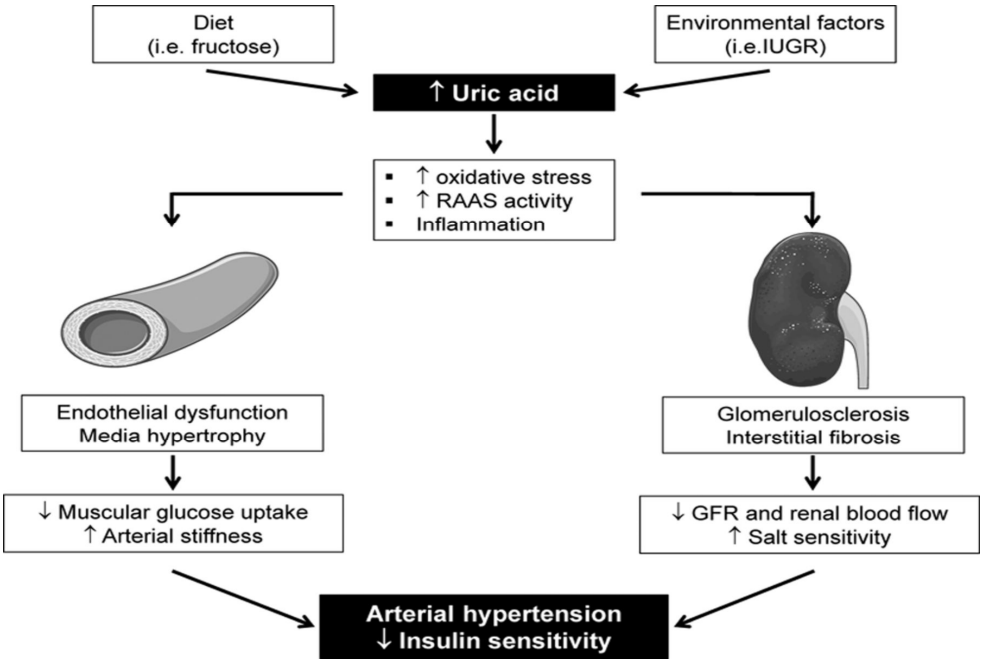

Fig 9. Uric acid in hypertension

Fructose rich diet and hyperuricemia:

Fructose rich diet is a contributory factor for the development of hyperuricemia. It is also evident that this pathological feature is not seen with the glucose rich diet. From the above context, it is clear that the component fructose has a major role to play in the development of metabolic syndrome. There are various scientific studies imparting this fact to light, it includes various studies conducted in animal models. They proved the statement to be true. The animals grown in the environment providing high fructose containing diet developed insulin resistance thought to be induced by the high fructode content in the diet provided to them. In the light of the study conducted by Nakagawa and collegues, it

was proved that hyperuricemia developed in the rat specimens not under uricase inhibitors and led to the onset of hyperinsulinemia, hypertriglyceridemia, hypertension, and obesity. In those models where allopurinol/ benzbromarone was early initiated failed to develop hyperuricemia and metabolic syndrome. It was also stated that the endothelial dysfunction could be controlled or reversed back to normal function by the administration of allopurinol (xanthine oxidase inhibitor). This fact reveals the role played by hyperuricemia in the development of endothelial dysfunction that could later lead to vascular remodelling, the final outcome of all these being the metabolic syndrome. Despite of these promising results, the use of allopurinol should be reduced as it could be the result of potential renal toxicity developed following administration of allopurinol.

The prevalence of obesity has remarkably increased in the Japanese, in relation to the usage of fructose rich corn syrup as a sweetener in the early 1970s. Initially, the trend of usage of these sweetening agents was only 1%, but in the current scenario the consumption of the fructose rich sweetening agent has increased to 40% in the United States of America, where it is now being used as a standard part of American diet. The trends in the incidence of CKD, hypertension and obesity in Americans has shown a relation to the usage of these

sweetening agents, and proved its part in the development of these disease conditions in the individuals.

It has also been demonstrated that, the kidney receiving high fructose gradually developed kidney failure, glomerulosclerosis and tubulointerstitial fibrosis. Similarly, Shoham *et.al* demonstrated an increased incidence of kidney related diseases in those individuals, who received high fructose containing diet. He related to the quantity of fructose consumed to the albumin excreted by the kidney. It was found in the study that the individuals consuming increased quantity of fructose had proteinuria which could be the indication of underlying pathology developing in the renal system. In support, Brymora *et.al* proved through a study that there was a fall in blood pressure and in the levels of the inflammatory markers in individuals with known chronic kidney disease, when provided with low fructose containing diet for 6 weeks. The mechanisms by which the fructose enhance the development of metabolic syndrome is complex to understand and cannot be explained only by obesity related pathways.

It is also worth to note that the administration of losartan attenuating the risk of kidney disease is demonstrated in a recently conducted study. The study included patients suffering from diabetic nephropathy. The uric acid levels decreases following administration of

losartan in them. With a decrease of uric acid level by 0.5mg/dl, the adverse effect on kidney by hyperuricemia reduced by 6%.

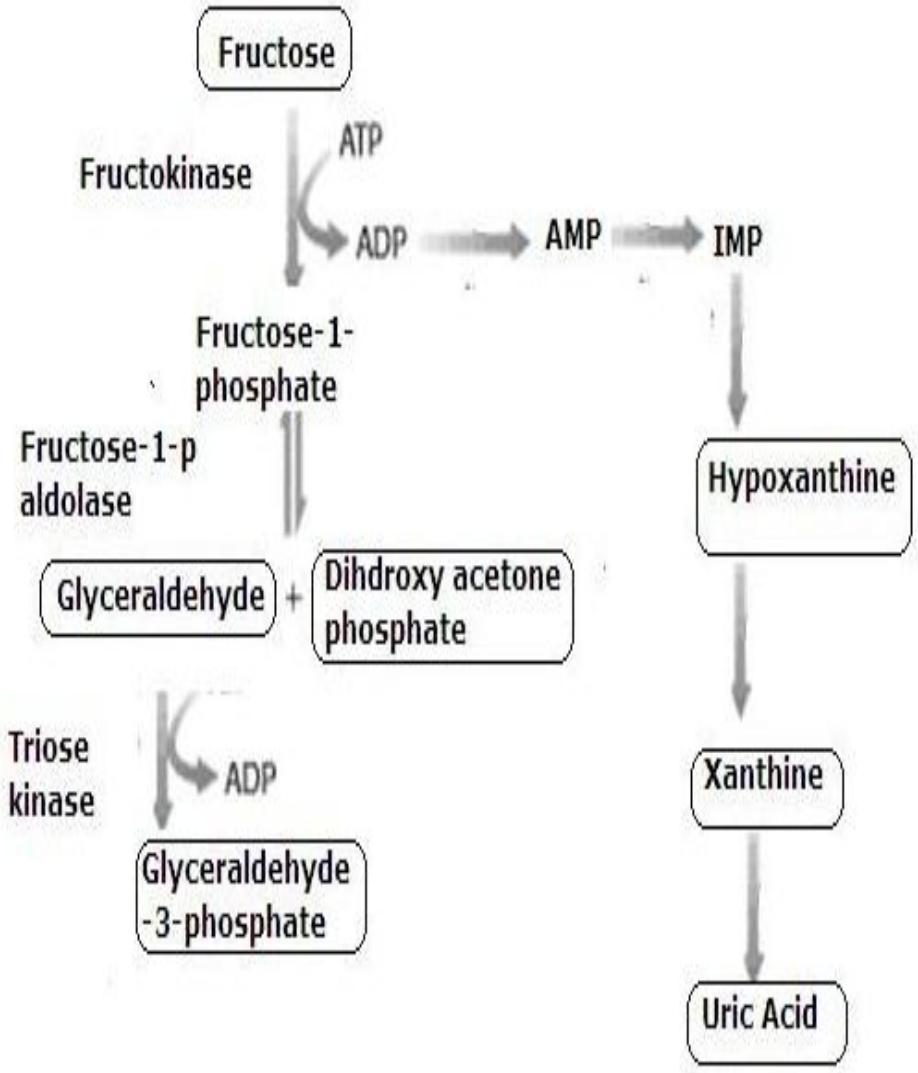

Fig.10 Fructose and hyperuricemia

MATERIALS AND METHODS

SOURCE OF STUDY

Data consists of primary data collected by the principal investigator directly from the patients who are admitted in the Government Coimbatore Medical College and Hospital.

DESIGN OF STUDY: Cross sectional study

PERIOD OF STUDY: One year, 2016- 2017.

SAMPLE SIZE: 100

100 patients with Metabolic syndrome components.

INCLUSION CRITERIA:

Patients above the age of 20 years with various metabolic syndrome components without prior history of cardiovascular disease, malignancy, stroke, kidney disease and gout.

EXCLUSION CRITERIA

1. Patients with gout
2. Patients with renal insufficiency(eGFR<60)
3. Patients on diuretic therapy

4. Patients with prior history of malignancy,cardiovascular disease,stroke,
5. Patients not capable of giving consent (psychiatric patients).
6. Patients not willing to participate in the study (who refused to consent)
7. Pregnant and lactating women.

METHODOLOGY

The study was undertaken on the patients attending medicine out patient department and admitted in the Coimbatore Medical College and Hospital, Coimbatore during the study period july 2016 to june 2017. A total of 100 patients with various newly diagnosed metabolic syndrome components were included in the study based on the inclusion/exclusion criteria.

The list of the patients enrolled in the study is appended along with the dissertation. The study excludes minors, pregnant women, mentally-ill and non-volunteering patients.

The study was conducted after obtaining informed signed consent from the patients. The duration of the study is one year from 2016 to 2017. The principal investigator, after obtaining informed signed consent from the patients to participate in the study, collected their baseline characteristic details and physical examination details to identify metabolic syndrome based on NCEP/ATP III criteria with guidelines for waist circumference adapted from IDF guidelines.

- Waist circumference->90cm for men,80cms for women
- TGL >150mg/dl
- Reduced HDL-C <50 for women and <40 for men

- BP > 130 systolic or 85 diastolic
- FBS >100mg/dl

3 or more components defines MetS.

Waist circumference was measured at midway between the xiphi sternum and anterior superior iliac spine with a non-stretchable measuring tape. Single layer of light cloth was allowed. Blood pressure was measured in both upper limbs with mercury sphygmomanometer and the average blood pressure was taken for the study purpose. A fasting venous blood sample was taken and sent to the central laboratory for fasting blood sugar, triglyceride, HDL cholesterol and serum uric acid levels. Blood urea and serum creatinine levels were also checked as a part of exclusion criteria for all patients. Anthropometric measurements of patients were used to calculate the body mass index of the patient. List of biochemical investigations done is as follows.

INVESTIGATIONS:

1. Serum uric acid
2. Fasting blood sugar level
3. Fasting triglycerides level
4. HDL cholesterol
5. Blood urea & serum creatinine

OBSERVATIONS AND RESULTS

The study population included 100 patients who met the inclusion crieteria and their base line biochemical parameters and anthropometric measurements were taken. The following observations were made and statistical analysis of the observations and values obtained was done.

Among the patients 51 were females and 49 were males.

SEX	NO OF PATIENTS	PERCENTAGE
MALE	49	49%
FEMALE	51	51%

Table 4. Sex distribution of study subjects

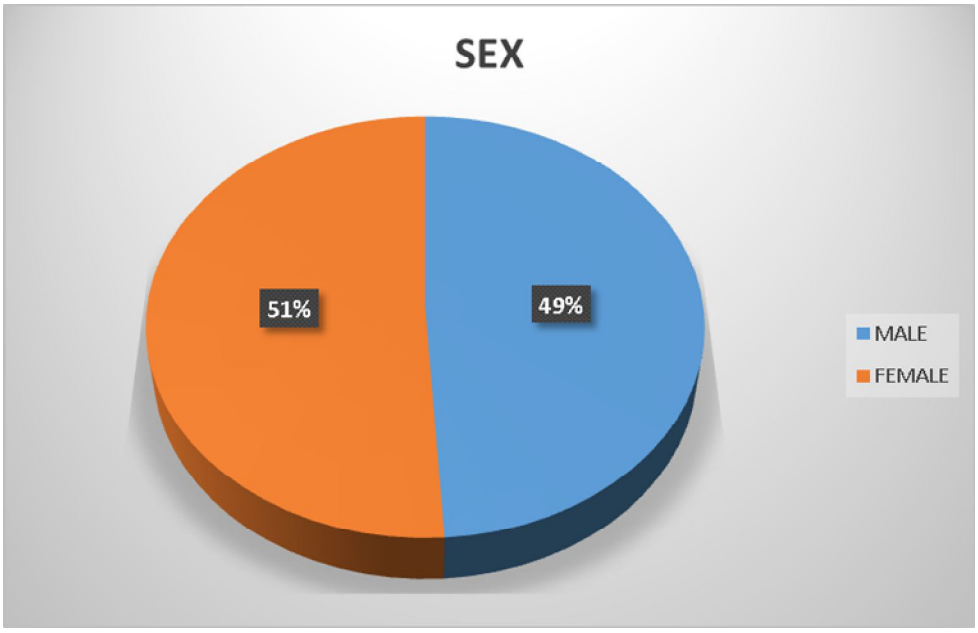

Chart 1. Sex distribution of study subjects

Among the females 25 patients had metabolic syndrome and 19 of the male patients were also identified to be having metabolic syndrome. The statistical analysis doesn't revealed any significant sex preponderance of metabolic syndrome.

		METABOLIC SYNDROME		TOTAL
		YES	NO	
SEX	MALE	19	30	49
	FEMALE	25	26	51
TOTAL		44	56	100
P VALUE - 0.302				
NON SIGNIFICANT				

Table 5. Correlation between sex and metabolic syndrome

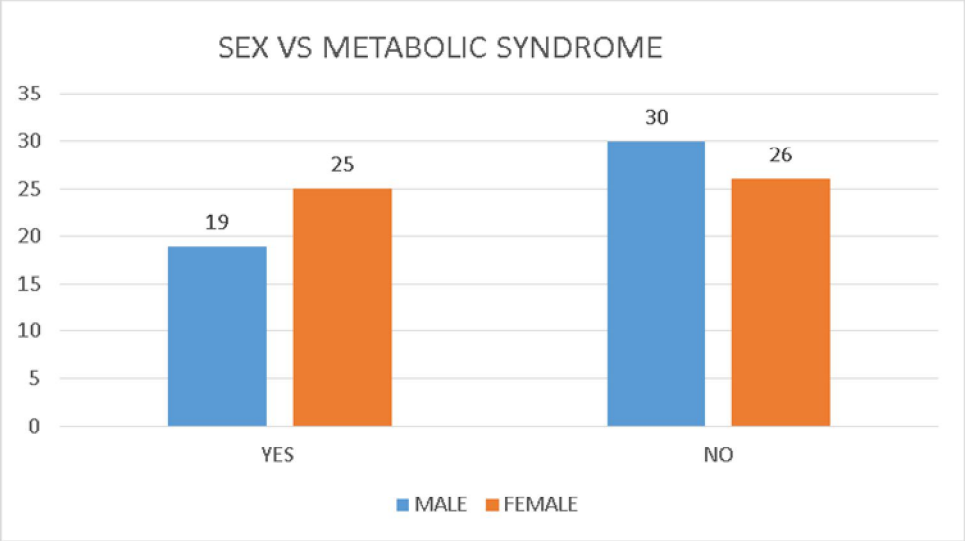

Chart 2. Sex and metabolic syndrome

Out of 100 patients 37 were normouricemic and 37 were hyperuricemic. Study revealed a female preponderance for hyperuricemia with 25 out of the total of 37 being hyperuricemic.

		SERUM URIC ACID		TOTAL
		HIGH	LOW	
SEX	MALE	12	37	49
	FEMALE	25	26	51
TOTAL		37	63	100
P VALUE - 0.011				
SIGNIFICANT				

Table 6. Sex and serum uric acid

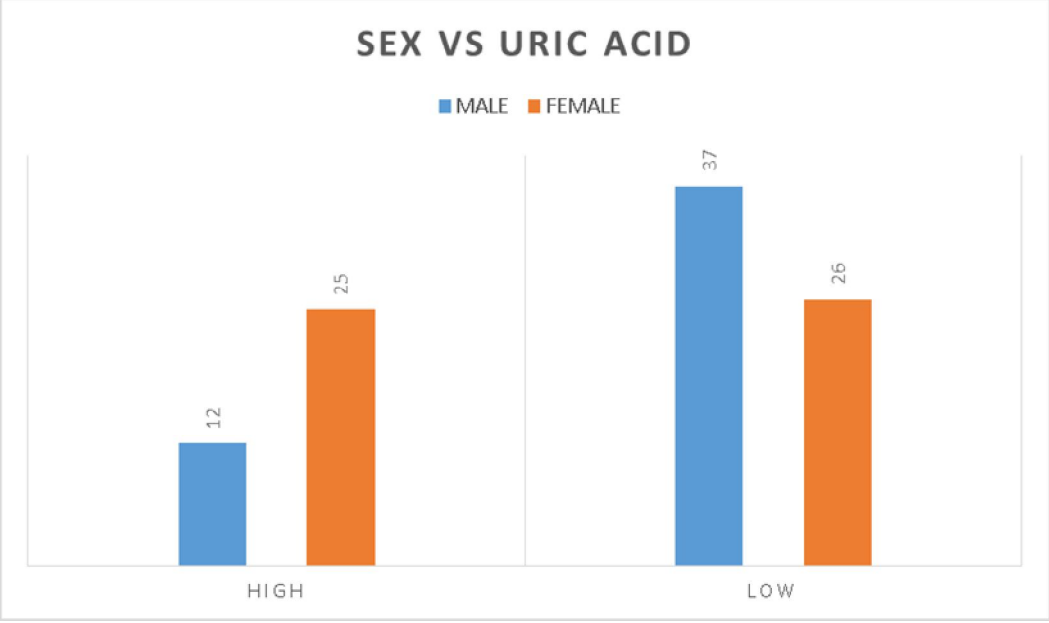

Chart 3.Sex and serum uric acid

The age wise distribution of the patients were as follows. Majority of the patients fall into the age group of 30 to 60 years with 83 people falling into the age group, with only 4 patients less than 30 and 13 members more than 60

AGE(IN YRS)	TOTAL NO OF PATIENTS
< 30	4
31-40	22
41-50	28
51-60	33
61-70	13

Table 7. Age distribution of study subjects

Most of the patients were clustered in the age group of 30 years to 60 years.

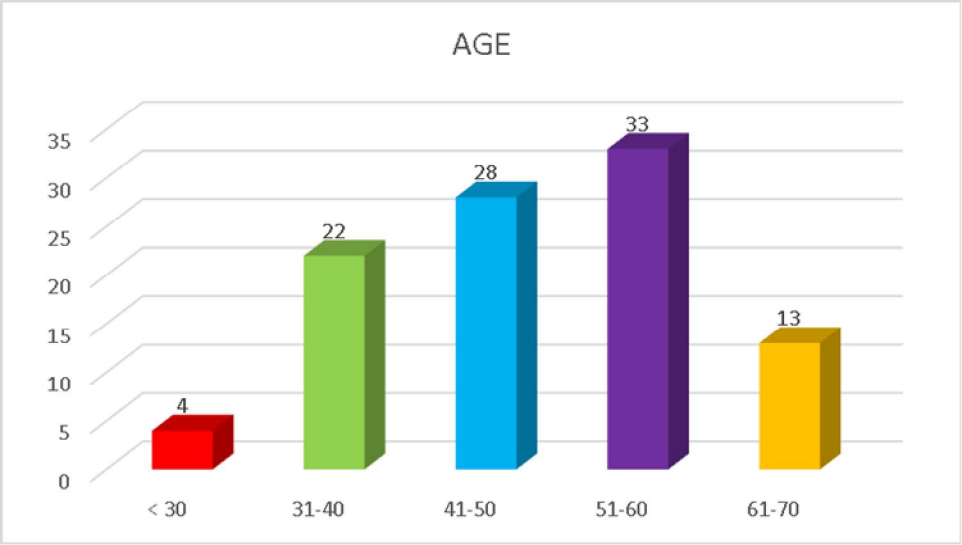

Chart 4.Age wise distribution of study subjects

The occurrence of metabolic syndrome was found to be higher in the age group of 40 year to 60 years. With less number of patients in the age group less than 30 years and more than 60 years

AGE(IN YRS)	METABOLIC SYNDROME		TOTAL NO OF PATIENTS
	PRESENT	ABSENT	
< 30	1	3	4
31-40	7	15	22
41-50	10	18	28
51-60	19	14	33
61-70	7	6	13

Table 8. Age wise distribution of metabolic syndrome

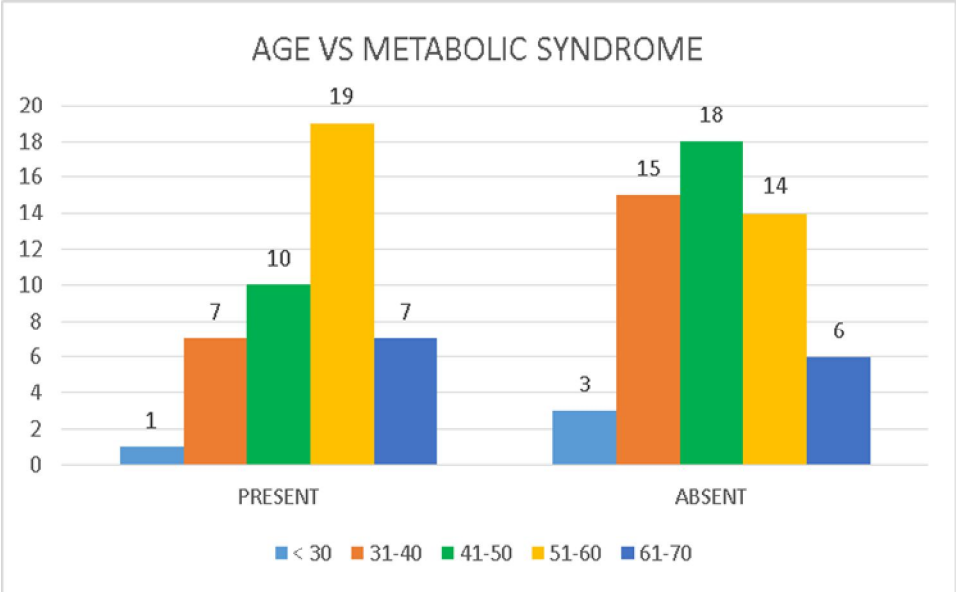

Chart 5. Age wise distribution of metabolic syndrome

Patients with hyperuricemia were mostly from the age group between 40 years to 60 years. With less number of patients falling into the age group less than 40 years and more than 60 years.

AGE(IN YRS)	URIC ACID		TOTAL NO OF PATIENTS
	HIGH	LOW	
< 30	1	3	4
31-40	5	17	22
41-50	6	22	28
51-60	19	14	33
61-70	6	7	13

Table 9. Age wise distribution of hyperuricemia

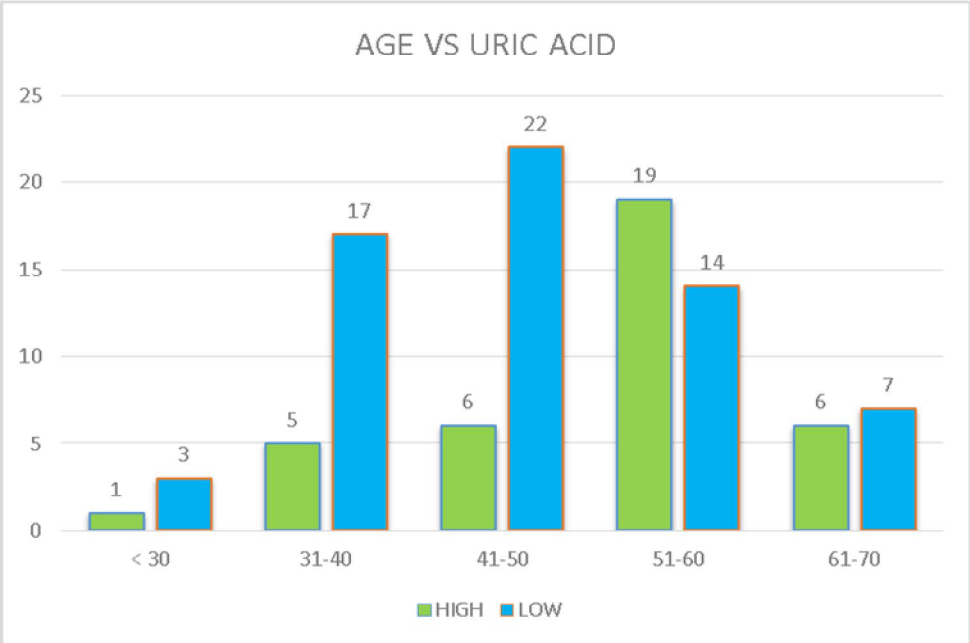

Chart 6. Age wise distribution of hyperuricemia

According to NCEP/ATP III criteria 44 among the 100 patients were found to have metabolic syndrome.

METABOLIC SYNDROME	NO OF PATIENTS
PRESENT	44
ABSENT	56

Table 10. Distribution of metabolic syndrome

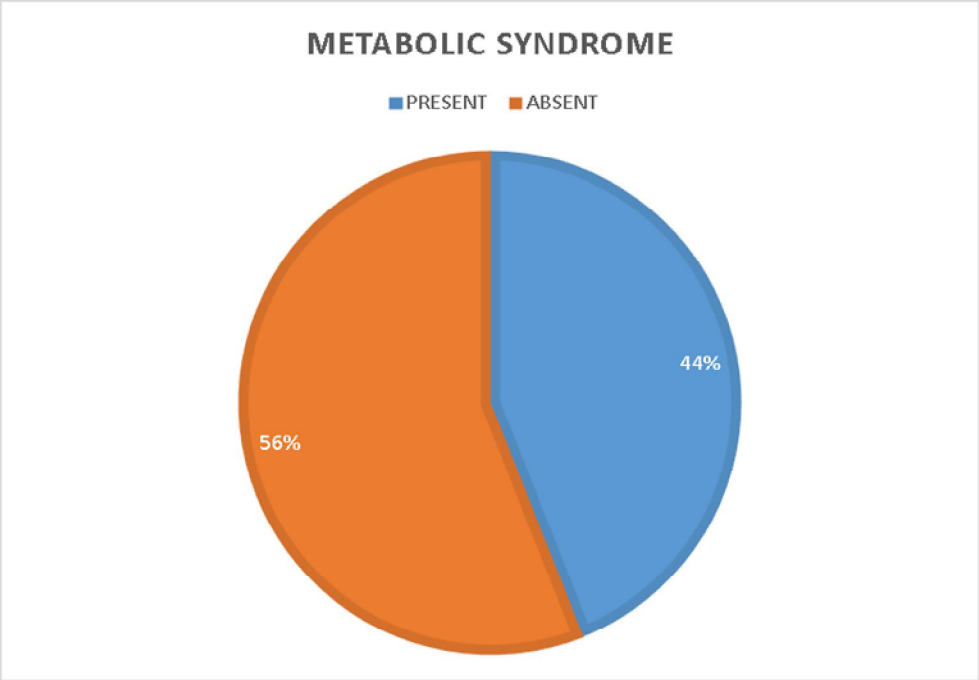

Chart.7 Distribution of metabolic syndrome

Hyperuricemia was present in 37 subjects out of 100.The cut off range for serum uric acid was taken as >=7mg/dL for men and >=6mg/dL fot women.

SERUM URIC ACID	NO OF PATIENTS
NORMAL	63
HIGH	37

Table 11.Distribution of hyperuricemia

The following chart shows the distribution of serum uric acid level

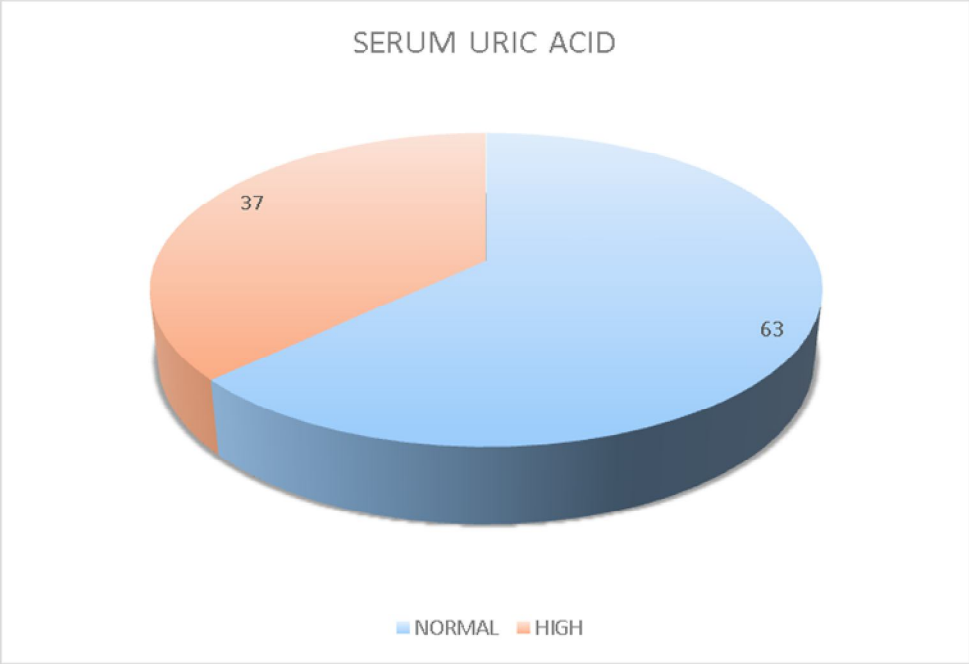

Chart 8. Distribution of hyperuricemia

The mean age among hyperuricemic subjects were 52.59 when compared to 46.43 in normouricemic subjects which was statistically significant with a p-value of 0.006

SERUM URIC ACID	AGE	
	MEAN	STANDARD DEVIATION
HIGH	52.59	9.86
LOW	46.43	10.94
P VALUE - 0.006		
SIGNIFICANT		

Table 12. Correlation between Age and serum uric acid

This chart shows the relationship between mean age and serum uric acid level.

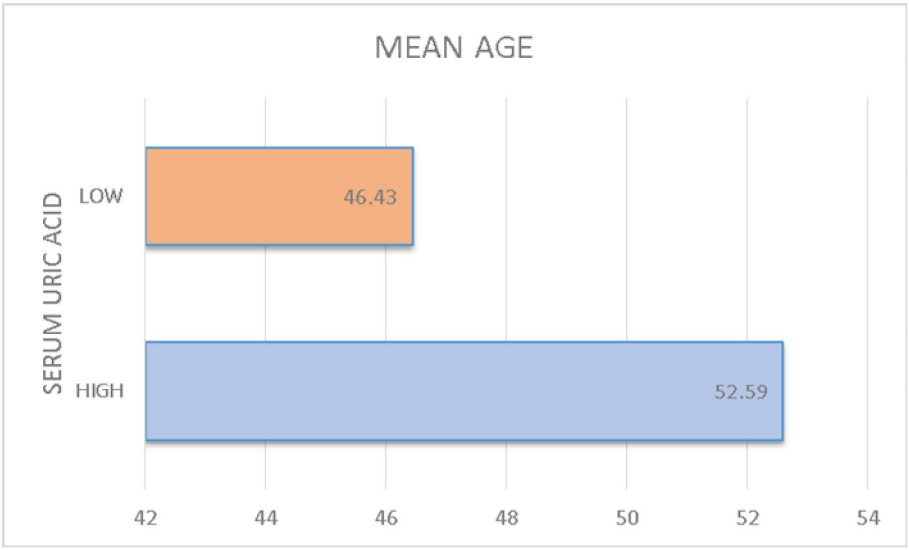

Chart 9. Mean age vs serum uric acid

The mean body mass index calculated was found to be significantly higher among people with hyperuricemia with a p-value of 0.001.The absolute values were 26.6 compared to 23.34.

SERUM URIC ACID	BODY MASS INDEX	
	MEAN	STANDARD DEVIATION
HIGH	26.6	3.51
LOW	23.34	2.46
P VALUE - 0.001		
SIGNIFICANT		

Table 13.Correlation between BMI and serum uric acid

This chart depicts the mean BMI in hyperuricemic and normouricemoic subjects

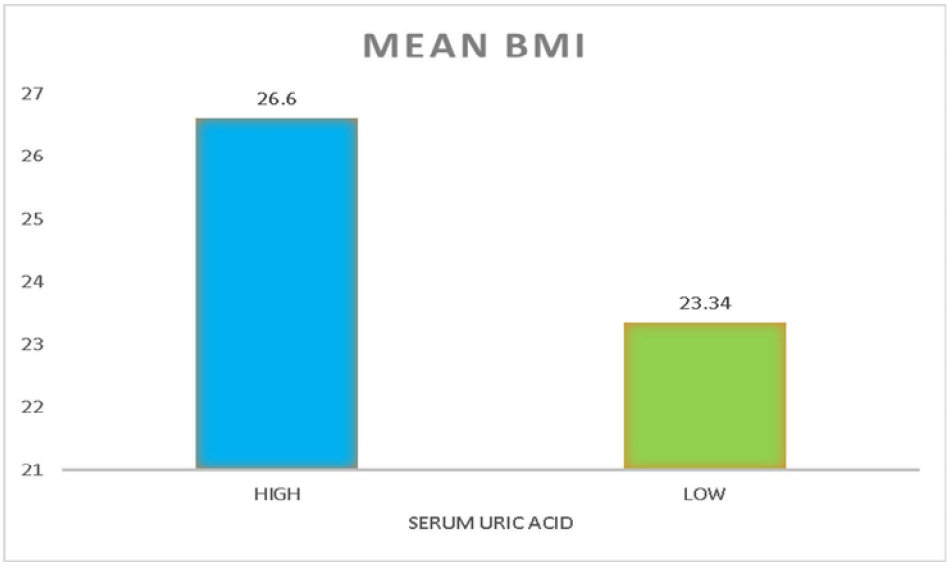

Chart 10.Mean BMI and serum uric acid

The odds ratio of high body mass index to the high serum uric acid was found to be 1.9, signifying the 1.9 times higher risk of having high BMI in hyperuricemic subjects.

SERUM URIC ACID	BODY MASS INDEX	
	HIGH	NORMAL
HIGH	33	4
LOW	32	31
ODDS RATIO - 1.9		

Table 14. Odds ratio of serum uric acid vs body mass index

This chart depicts the above relationship.It clearly shows people with higher serum uric acid are having high body mass index.33 out of the 37 hyperuricemic subjects are having their BMI above the cut of range.

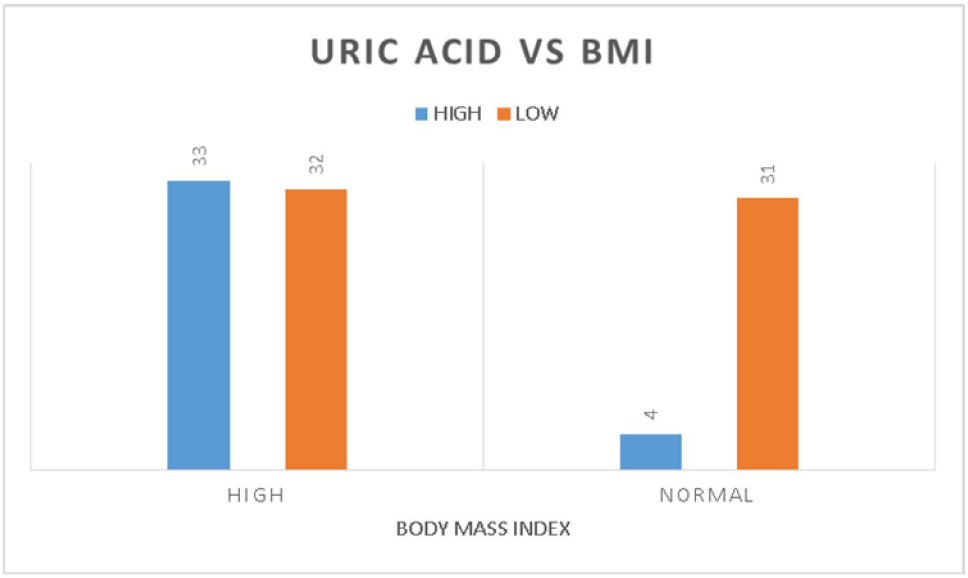

Chart.11 Odds ratio of serum uric acid to BMI

The mean systolic blood pressure was found to be higher among people with hyperuricemia, when compared to people with normal serumuric acid levels. Which was found to be statistically significant with a p-value of 0.001.

SERUM URIC ACID	SYSTOLIC BLOOD PRESSURE	
	MEAN	STANDARD DEVIATION
HIGH	154	19.93
LOW	129.78	16.67
P VALUE - 0.001		
SIGNIFICANT		

Table 15. Mean BMI vs Serum uric acid

This chart shows the correlation between serum uric acid and mean systolic blood pressure.

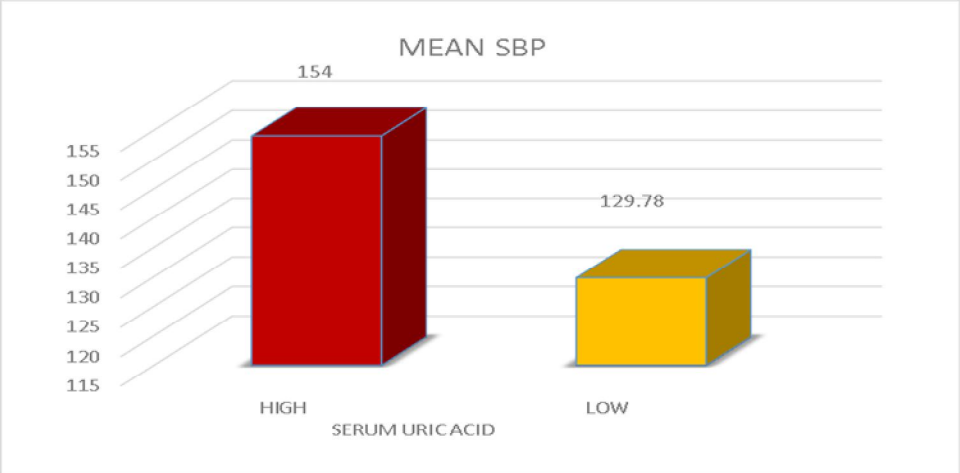

Chart 12. Mean SBP vs Serum uric acid

The odds of a hyperuricemic patient to have high systolic blood pressure was found to be 6.6, stating a 6.6 times higher risk.

SERUM URIC ACID	SYSTOLIC BLOOD PRESSURE	
	HIGH	NORMAL
HIGH	32	5
LOW	31	32
ODDS RATIO - 6.6		

Table 16. Odds ratio of serum uric acid vs systolic blood pressure

This bar diagram shows 32 out of the 37 patients with hyperuricemia was having the systolic blood pressure above the cut of value.

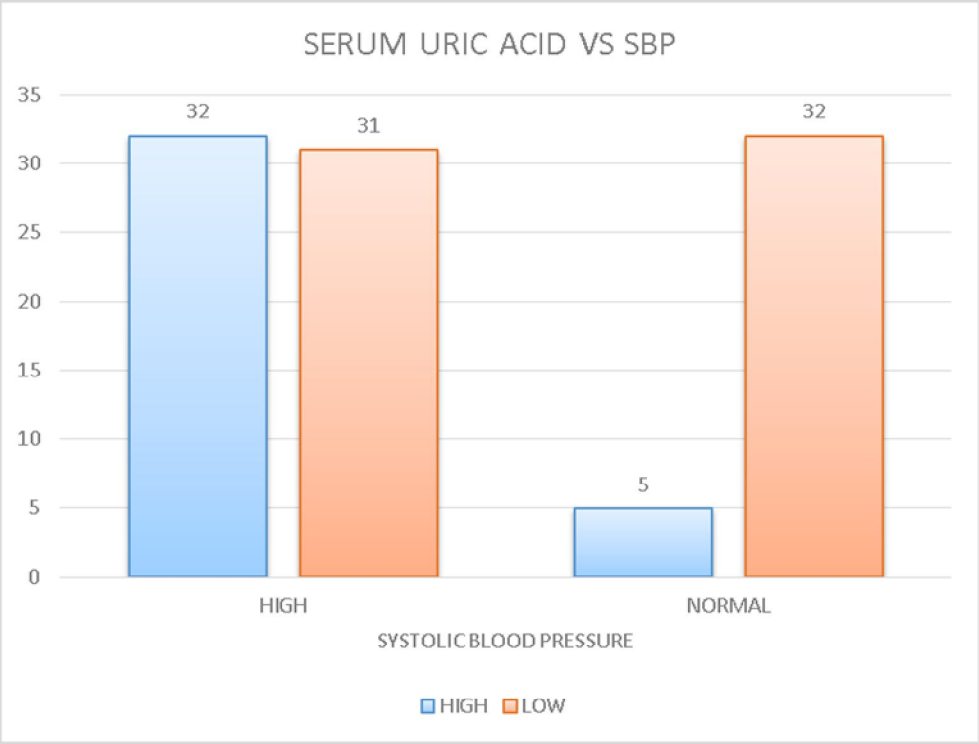

Chart 13.Odds ratio of serum uric acis to systolic blood pressure

The mean diastolic blood pressure was also higher among people having hyperuricemia, which was statistically significant with a p-value of 0.001

SERUM URIC ACID	DIASTOLIC BLOOD PRESSURE	
	MEAN	STANDARD DEVIATION
HIGH	94.76	11.52
LOW	80.79	11.02
P VALUE - 0.001		
SIGNIFICANT		

Table 17.Mean diastolic BP vs serum uric acid

This chart shows the correlation between mean diastolic blood pressure and serum uric acid.

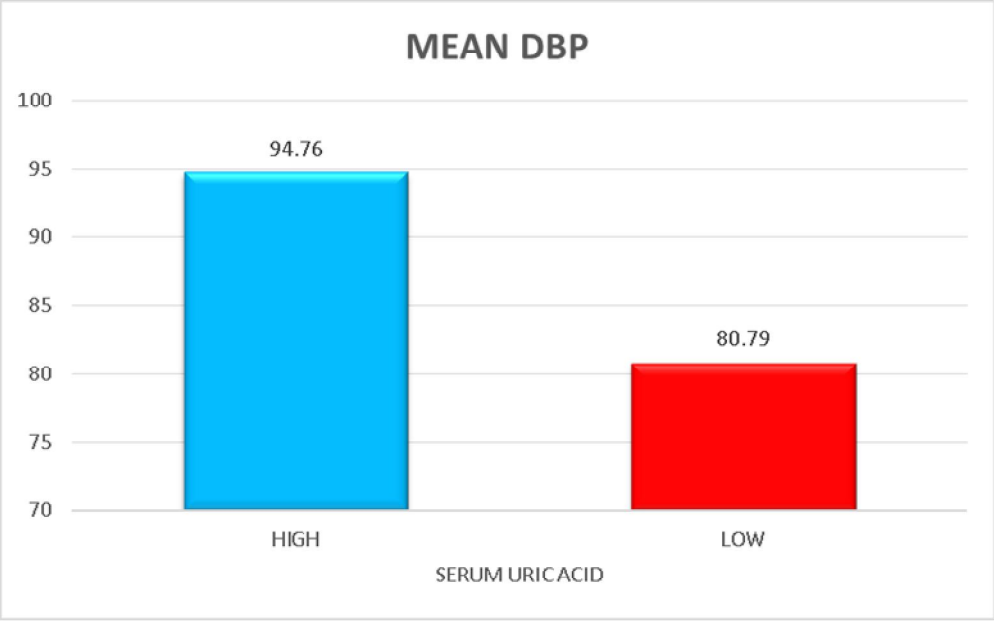

Chart 14.Mean diastolic BP vs Serum uric acid

The odds ratio between diastolic blood pressure and serum uric acid is found to be 2.26, indicating a 2.26 times higher risk of diastolic hypertension among the people with higher serum uric acid level.

SERUM URIC ACID	DIASTOLIC BLOOD PRESSURE	
	HIGH	NORMAL
HIGH	29	8
LOW	23	40
ODDS RATIO - 2.26		

Table 18.Odds ratio of diastolic BP to serum uric acid

This chart shows the odds ratio of high diastolic blood pressure to high serum uric acid level.

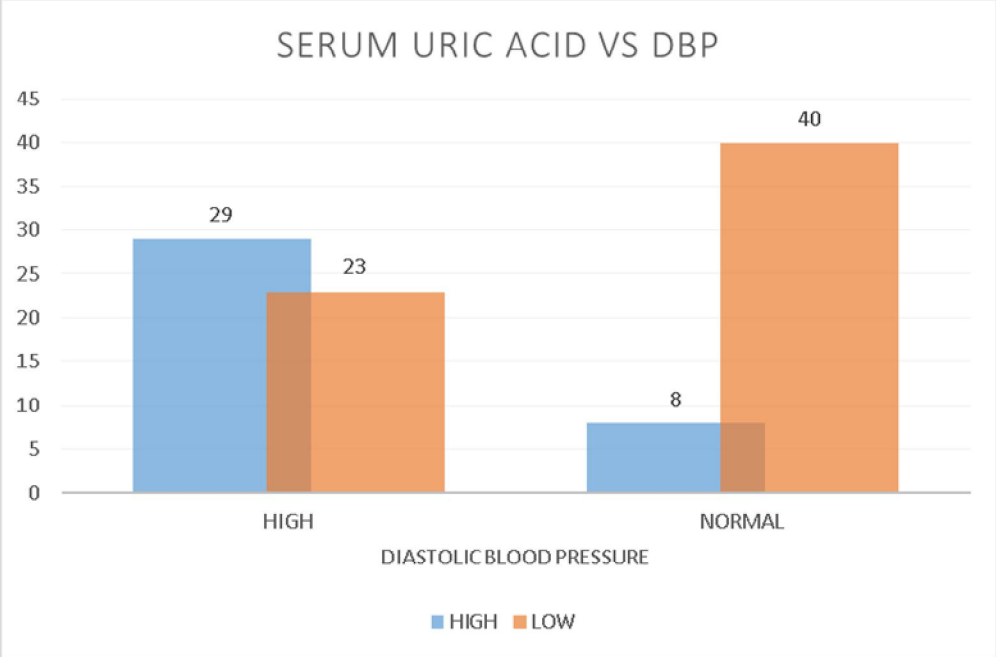

Chart 15.Odds ratio of diastolic BP to serum uric acid

The fasting blood sugar level was found to be high among the hyperuricemic subjects,which is statistically significant with a p-value of 0.001

SERUM URIC ACID	FASTING BLOOD SUGAR	
	MEAN	STANDARD DEVIATION
HIGH	152.92	53.44
LOW	104.7	33.84
P VALUE - 0.001		
SIGNIFICANT		

Table19.Fasting blood sugar vs serum uric acid

This chart shows the relationship between mean fasting triglyceride level to serum uric acid.

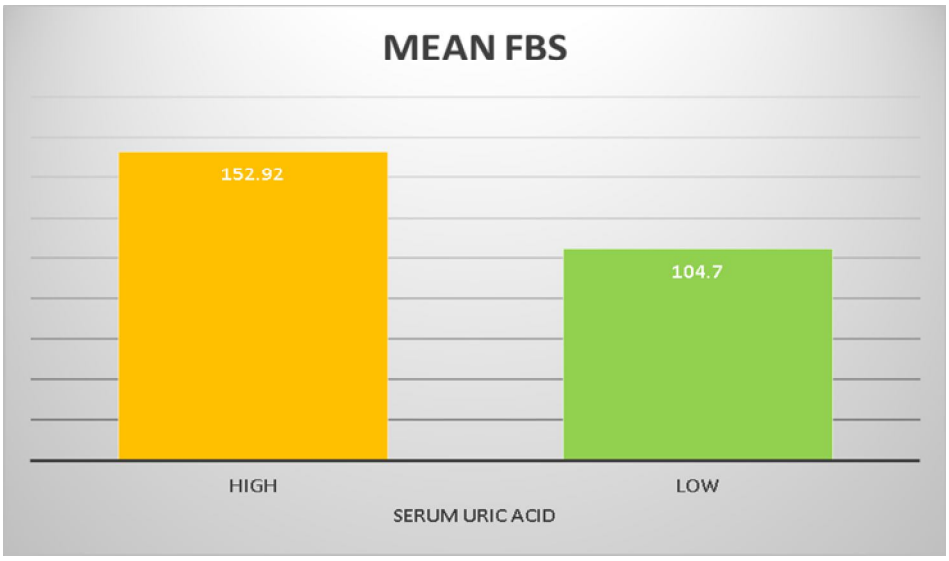

Chart 16.Fasting blood sugar vs serum uric acid

The odds ratio of fasting blood sugar to serum uric acid was calculated to be 5.8, indicating 5.8 times higher risk of having hyperglycemia in hyperuricemia.

SERUM URIC ACID	FASTING BLOOD SUGAR	
	HIGH	NORMAL
HIGH	27	10
LOW	20	43
ODDS RATIO - 5.8		

Table20.Odds ratio of fasting blood sugar to serum uric acid

This chart shows the odds of high serum uric acid level to have high fasting blood sugar.

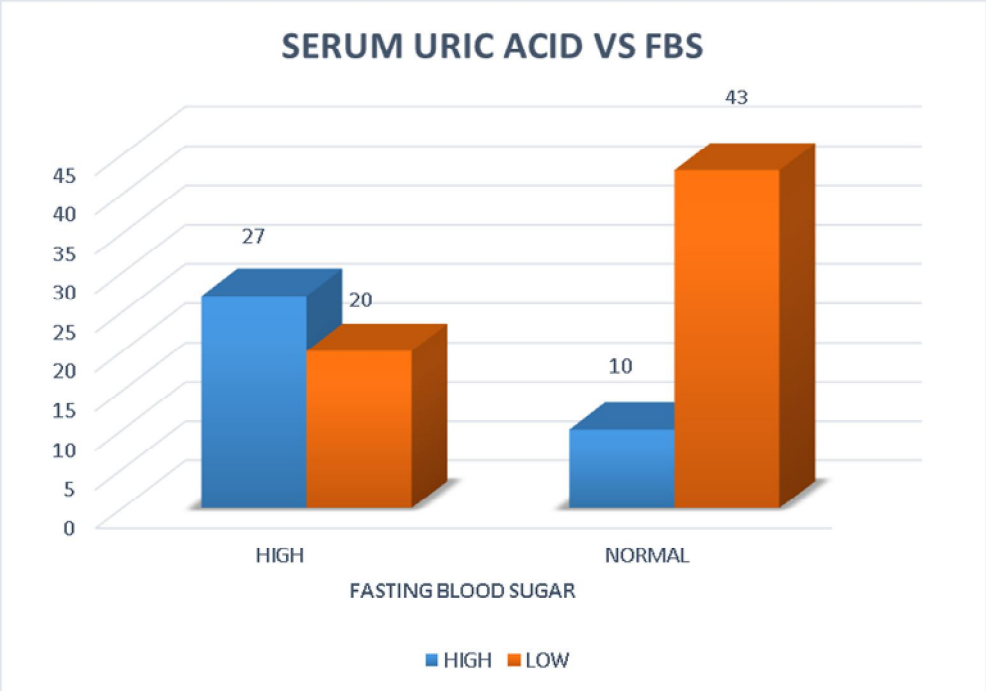

Chart 17.Odds ratio of fasting blood sugar to serum uric acid

The mean waist circumference was 91.11cm in hyperuricemic subjects against 85.57cm in normouricemic subjects, which is statistically significant with a p-value of 0.006

SERUM URIC ACID	WAIST CIRCUMFERENCE	
	MEAN	STANDARD DEVIATION
HIGH	91.11	12.86
LOW	85.57	6.81
P VALUE - 0.006		
SIGNIFICANT		

Table21. Mean waist circumference vs serum uric acid

This chart shows the relationship between mean waist circumference and serum uric acid level

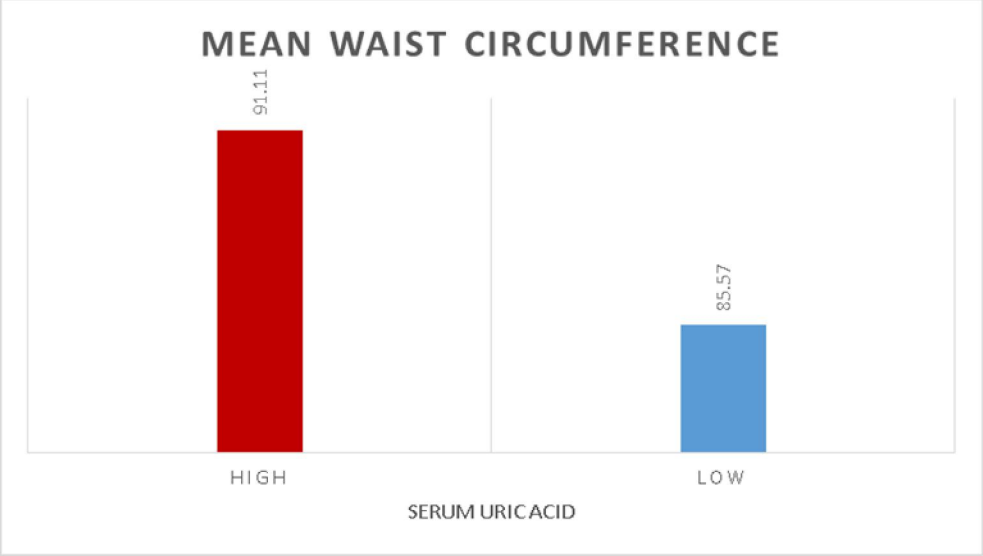

Chart 18. Mean waist circumference to serum uric acid

The odds ratio between waist circumference and serum uric acid is calculated to be 2.26, indicating 2.26 times higher chance of having high waist circumference in hyperuricemic patients.

SERUM URIC ACID	WAIST CIRCUMFERENCE	
	HIGH	NORMAL
HIGH	19	18
LOW	20	43
ODDS RATIO - 2.26		

Table 22.Odds ratio between waist circumference and serum uric acis

This chart shows the odd of a hyperuricemic to have high waist circumference.

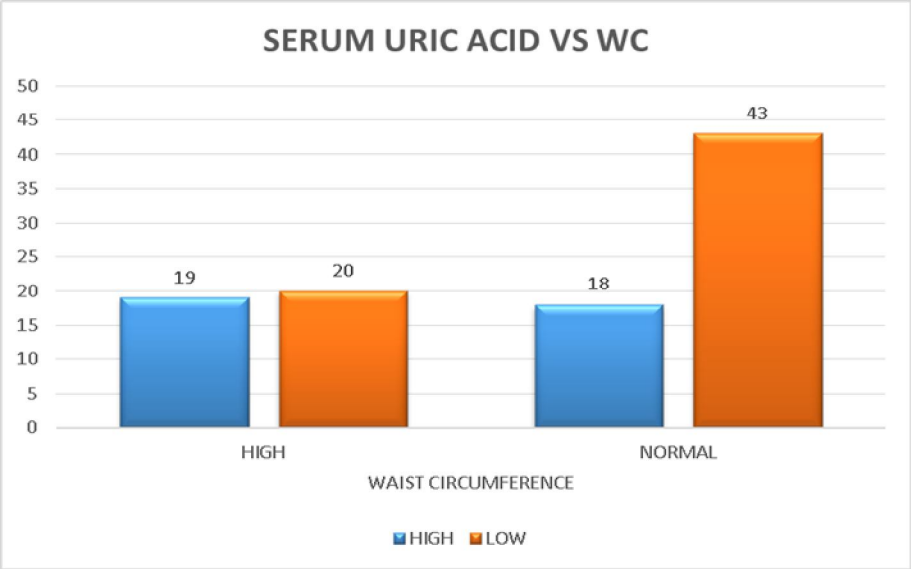

Chart 19.Odds ratio of waist circumference to serum uric acid

The mean triglyceride level was higher among the hyperuricemic subjects, which was statistically significant.

SERUM URIC ACID	TRIGLYCERIDES	
	MEAN	STANDARD DEVIATION
HIGH	165.24	27.37
LOW	146.37	24.47
P VALUE - 0.001		
SIGNIFICANT		

Table 23. Mean triglycerides vs serum uric acid

This chart shows the relationship between mean triglyceride to serum uric acid.

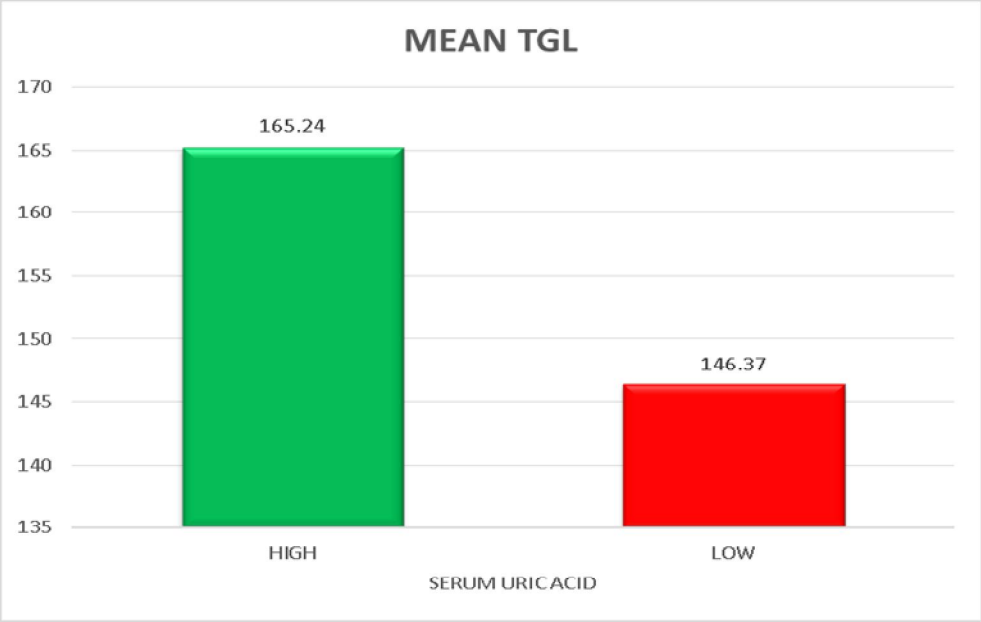

Chart 20.Mean triglycerides to serum uric acid

The odds ratio of serum uric acid to serum triglycerides is found to be 6.3, indicating a 6.3 times higher risk of hypertriglyceridemia among patients with hyperuricemia.

SERUM URIC ACID	TRIGLYCERIDES	
	HIGH	NORMAL
HIGH	29	8
LOW	23	40
ODDS RATIO - 6.3		

Table 24.Odds ratio of triglycerides to serum uric acid

This chart shows the odds of a hyperuricemic patient to have high serum triglyceride level.

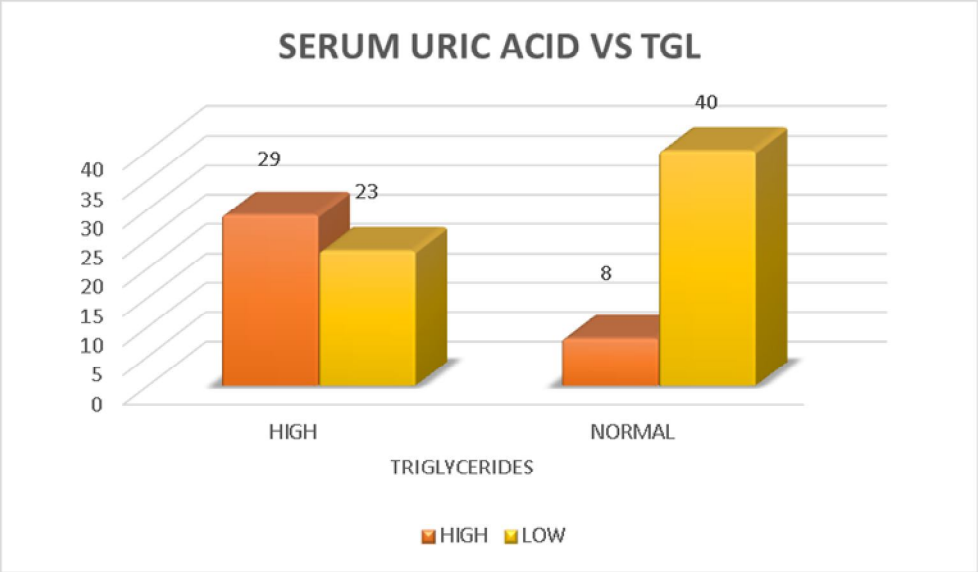

Chart 21. Odds ratio of serum uric acid to triglycerides

The mean HDL level, even though found to be higher among people with higher uric acid level, it was not statistically significant.

SERUM URIC ACID	HIGH DENSITY LIPOPROTEIN	
	MEAN	STANDARD DEVIATION
HIGH	41.24	8.43
LOW	45.48	8.75
P VALUE - 0.061		
NON SIGNIFICANT		

Table 25.Mean HDL vs serum uric acid

This chart shows the relationship between mean HDL and serum uric acid

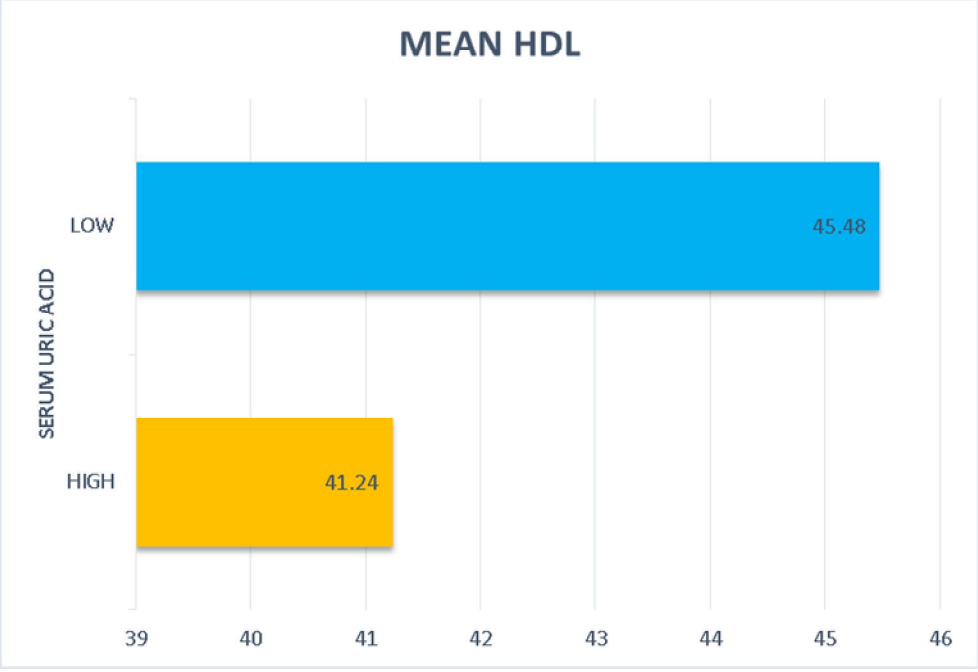

Chart 22.Mean HDL vs serum uric acid

There is 2.96 times higher risk of having a low HDL cholesterol level in hyper uricemic patients when compared to the normouricemic group as depicted by an odds ratio of 2.96

SERUM URIC ACID	HIGH DENSITY LIPOPROTEINS	
	LOW	NORMAL
HIGH	25	12
LOW	26	37
ODDS RATIO - 2.96		

Table 26. Odds ratio of serum uric acid to HDL

This chart shows the odds of a hyperuricemic patient to have high serum HDL level

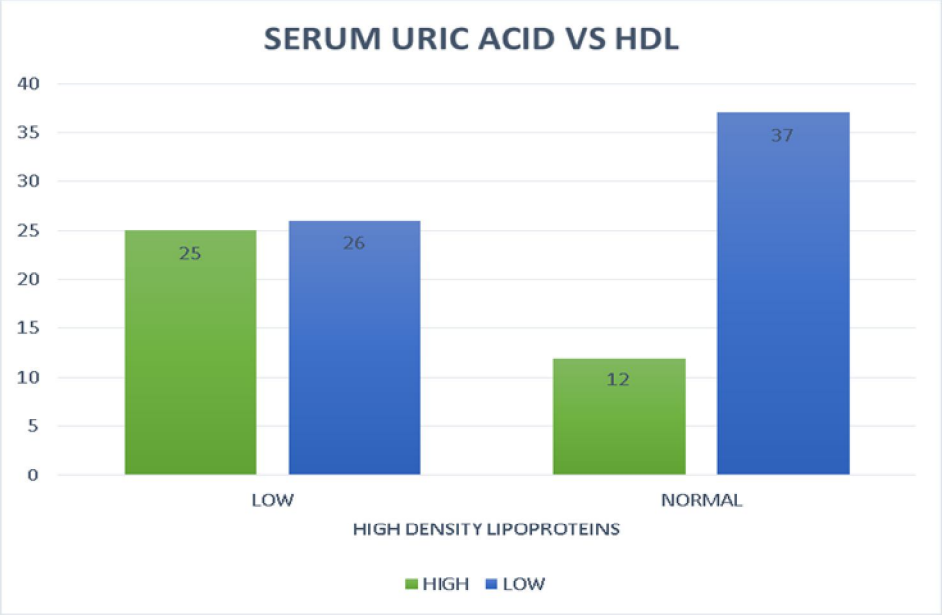

Chart 23 Odds ratio of serum uric acid to HDL

The mean number of metabolic syndrome components were significantly higher among people with hyperuricemia with p-value of 0.001

SERUM URIC ACID	METABOLIC SYNDROME COMPONENTS	
	MEAN	STANDARD DEVIATION
HIGH	3.49	0.83
LOW	1.79	0..74
P VALUE - 0.001		
SIGNIFICANT		

Table 27.Number of Metabolic syndrome components to serum uric acid

This chart shows the relationship between mean number of metabolic syndrome components and sserum uric acid level

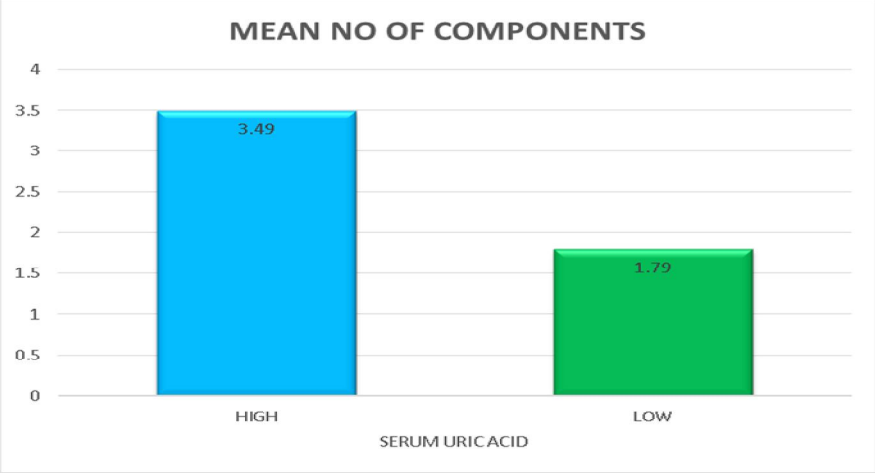

Chart 24.Mean metabolic syndrome components to serum uric acid

DISCUSSION

Metabolic syndrome comprises a cluster of risk factors rather than disease per say, which predisposes a patient to various cardiovascular and cerebrovascular events. Identifying metabolic syndrome becomes important in this perspective; patient and public awareness to the risk factors causing non communicable diseases is utmost important in the current scenario.

My study was conducted among 100 patients who attended OPD as well as IPD of Coimbatore medical college during the year 2016-2017. All of them had at least one of the five components of metabolic syndrome and the presence of other components were actively searched. Relationship of each of these components with serum uric acid were searched for, using appropriate statistical methods.

51 female and 49 male patients were selected based on inclusion and exclusion criteria and informed consent was obtained from them. Various clinical parameters and biochemical parameters like Blood pressure, fasting blood sugar, Triglyceride level, HDL cholesterol, waist circumference, height and weight were measured and BMI was calculated. Among the 100 patients 19 of the males and 25 of the females were identified to have metabolic syndrome based on NCEP/ATP III criteria with waist circumference values adapted from ADA guidelines.

Hyperuricemia was defined as serum uric acid level of >/=7mg/dL in males and >/=6mg/dL in females. Total of 37 patients were identified to be having hyperuricemia out of which 12 were males and 25 were females and with a significant sexual preponderance to females with a p-value of 0.011.

Most of the study subjects were within the age group of 30 to 60 years. Metabolic syndrome was mostly clustered in the age group of 40 to 60 years and Hyperuricemia was also clustered in the same age group. The mean age among the hyperuricemic subjects was 52.59 compared to the 46.43 in the normouricemic subjects, which was found to be statistically significant with a p-value of 0.006.

The mean body mass index among the hyperuricemic patients was 26.6 compared to the 23.34 of normouricemic patients which was statistically significant with a p-value of 0.001. The odds ratio of the above parameters were found to be 1.9, which indicates 1.9 times higher risk of developing high BMI in hyperuricemic subjects when compared to normouricemic subjects. Mean systolic blood pressure among the hyperuricemic subject were 154 mmHg compared to 129.78 mmHg of normouricemic patients which was statistically significant with a p-value of 0.001. The odds ratio of systolic blood pressure to serum uric acid level was found to be 6.6, which implies that there is 6.6 times higher risk

for developing systolic hypertension in hyperuricemic patients than the ones who have a normouricemic condition.

The mean diastolic blood pressure was also significantly higher among the first group with 94.76mmHg compared to 80.29mmHg with a p-value of 0.001.Odds ratio of the above parameters was calculated to be 2.26, which means that, there is 2.26 times more risk for developing diastolic hypertension among people with higher serum uric acid levels. Mean Fasting blood sugar also showed significant correlation with serum uric acid with 152.92 mg/dL in hyperuricemic 146.37 mg/dL in normouricemic subjects with a p-value of 0.001.The odds ratio also correlates well with a value of 5.8, indicating 5.8 times higher risk for developing diabetes in hyperuricemic individuals.

Waist circumference was found to be higher among hyperuricemic patients compared to normouricemic patients-91.11 cm to 85.57cm and was statistically significant with a p-value of 0.006.Odds ratio was found to be 2.26, which indicates there is 2.26 times higher risk of a hyperuricemic subjects to have elevated waist circumference compared to people with normal serum uric acid level.

Mean triglycerides level was found to be 165.24 mg/dL in hyperuricemic subject when compared to 146.37 mg/dL in normouricemic subject which was statistically significant with a p-value

of 0.001.The odds ratio was calculated to be 6.3, with a 6.3 times higher risk. HDL cholesterol levels failed to show a significant correlation with serum uric acid levels with a 41.24 mg/dL in the hyperuricemic group compared to the 45.48 mg/dL in the normouricemic group with a p-value of 0.06. Conversely the odds ratio for serum HDL level was 2.96, which implies there is 2.96 times more chance that a hyperuricemic subject to have low HDL levels compared to normouricemic subjects.

Number of metabolic syndrome components increased significantly among hyperuricemic patients, they had average 3.49 components compared to 1.79 components present in normouricemic subjects, which is statistically significant with a p-value of 0.001.

Prevalence of hyperuricemia was 75% among the patients with metabolic syndrome .33 out of 44 patients with metabolic syndrome had hyper uricemia. The possible cut of levels above which incidence of metabolic syndrome become high was found to be 7.2 mg/dL for males and 6.8 mg/dL for females.

Out of five components of metabolic syndrome systolic blood pressure, diastolic blood pressure, Fasting blood glucose and triglyceride level showed significant correlation with serum uric acid while waist circumference and HDL cholesterol, even though followed the trend, failed to show any significant correlation with statistical analysis.

SUMMARY

Metabolic syndrome, being a cluster of risk factors for both cardiovascular and cerebrovascular events, need to be identified early and appropriate preventive measures to be taken. Recent evidences suggest importance of uric acid being a novel component of the metabolic syndrome. Its correlation with various components have been studied separately all over the world, but there are only limited studies available taking all components of metabolic syndrome into consideration.

In my study I have made an attempt to find a correlation between serum uric acid level and the various components of metabolic syndrome. The study was carried out on patients attending OPD and IPD of Coimbatore medical college during the year 2016 to 2017 after obtaining informed consent.

The study subjects were selected carefully based on the inclusion and exclusion criteria. The various components of the metabolic syndrome were actively searched among the patients and presence of metabolic syndrome was defined by the presence at least three of the five components according to NCEP/ATP III guidelines with the waist circumference cut off modified according to the latest ADA guidelines applicable to the south Asian population. Height and weight of all the

subjects were taken Serum uric acid level was measured in all the study subjects and body mass index was calculated.

Out of five components of metabolic syndrome systolic and diastolic blood pressure, fasting blood sugar, triglyceride level and waist circumference showed positive correlation with serum uric acid levels which were statistically significant. Patients Body mass index also significantly correlated with serum uric acid level while HDL levels were not significantly correlated with the serum uric acid levels. Odds ratio calculated showed an increased risk of developing various metabolic syndrome components among hyperuricemic patients.

The prevalence of metabolic syndrome in patients with hyperuricemia was found to be 75%. The cut off value of serum uric acid level above which risk of metabolic syndrome significantly raised was found to be 7.2mg for males and 6.8mg for females.

In conclusion serum uric acid can be made a mandatory investigation in patients who has any of the five components of metabolic syndrome. If hyperuricemia identified and an attempt can be made to identify other components of metabolic syndrome. These kind of patients maybe actively followed up for the development of new components and cardiovascular and cerebrovascular complications. Whether drugs that lower serum uric acid levels can actually prevent the development of new

components and correcting hyperuricemia is beneficial in preventing complications, effect of appropriate anti-diabetic drugs, lipid lowering agents, anti-hypertensives and active weight reduction on serum uric acid level is beyond the scope of this study and it needs further research activity.

CONCLUSION

1. Serum uric acid level statistically well correlated with Systolic blood pressure, Diastolic blood pressure, Fasting blood sugar, Serum triglyceride levels, Waist circumference and Body mass index.

2. HDL cholesterol level even though showed positive correlation with serum uric acid level, statistically significant correlation was not obtained.

3. The prevalence of hyperuricemia among patients with metabolic syndrome was found to be 75%.

4. Serum uric acid can be considered as an additional investigation who present with any of the metabolic syndrome components, and if hyperuricemia is found an active search for other risk factors to be made.

5. Serum uric acid level can also be considered as a part of regular follow up of patients with any of the metabolic syndrome components and hyperuricemic patients to be carefully monitored for the development of cardiovascular complications.

6. Whether drugs that lower serum uric acid levels can actually prevent the development of new components and correcting hyperuricemia beneficial in preventing complications, effect of appropriate anti-diabetic drugs, lipid lowering agents, anti-hypertensives and active weight reduction on serum uric acid level is beyond the scope of this study and it needs further research activity.

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ANNEXURE 1

CASE PROFORMA

Name: Sex:

Age : OP/IP Number:

Address:

Comorbid illness:

S.Uric acid:

FBS:

BP :

TGL:

HDL:

W.C:

Height:

Weight:

BMI:

B.Urea

Sr.Creatinine

ANNEXURE -2

CONSENT FORM

Yourself Mr./Mrs./Ms…….. are being asked to be a participant in the research study titled "**A CORRELATIVE STUDY BETWEEN SERUM URIC ACID LEVEL AND COMPONENTS OF METABOLIC SYNDROME"** in CMC Hospital, Coimbatore, conducted by DR.SARATH HARIDAS, Post Graduate Student, Department of General Medicine, Coimbatore Medical College. You are eligible after looking into the inclusion criteria. You can ask any question you may have before agreeing to participate.

Research Being Done

Uric acid as a prognostic marker in heart failure

Purpose of Research

To identify the role of uric acid as a prognostic marker in heart failure

Decline from Participation

You have the option to decline from participation in the study existing protocol for your condition.

Privacy and Confidentiality

Privacy of individuals will be respected and any information about you or provided by you during the study will be kept strictly confidential.

Authorization to publish Results

Results of the study may be published for scientific purposes and/or presented to scientific groups, however you will not be identified.

Statement of Consent

I volunteer and consent to participate in this study. I have read the consent or it has been read to me. The study has been fully explained to me, and I may ask questions at any time.

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Signature /Left thumb impression Date

(volunteer)

---------- ----------

Signature of witness Date

ஒப்புதல்படிவம்

பெயர் :

வயது:

பாலினம்:

முகவரி:

கோவை அரசு மருத்துவக் கல்லூரி மருத்துவமனையில் மருத்துவர் ruj;Qhjh!;தலைமையில் நடைபெறும் இந்த ஆய்வில் முழுசம்மதத்துடன் கலந்து கொள்ள சம்மதிக்கிறேன். இந்த ஆய்வில் என்னை பற்றி விவரங்களை பாதுகாப்புடன் இந்த ஆய்வில் வெளியிட ஆட்சேபணை இல்லை என்று தெரிவித்துக் கொள்கிறேன். எந்த நேரத்திலும் ஆய்வில் இருந்து எந்த நேரத்திலும் விலக்கிக் கொள்ளும் உரிமை உண்டு என்று அறிவேன்.

இடம்:

தேதி: கைகெயாப்பம்/ரேகை

KEY TO MASTER CHART

S URIC ACID	-	Serum Uric Acid
Weight (Kg)	-	Weight in Kilogram
Height (Mt)	-	Height in Metres
BMI	-	Body Mass Index
BP	-	Blood Pressure
FBS	-	Fasting Blood Sugar
WC	-	Waist Circumference
S.TGL	-	Serum Triglycerides
HDL	-	High Density Lipoprotein
NO. MS COM	-	Number of Components of Metabolic Syndrome
M.S	-	Metabolic Syndrome

MASTER CHART

SL.NO	Name	Age	Sex	S.Uric acid(mg/dl)	Weight(kg)	Height(Mtr)	BMI	BP	FBS	W.C	S.TGL	HDL	No.MS components	M.S
1	KANAGARAJ	45	M	6.2	63	1.72	21.3	150/100	95	94	123	55	2	NO
2	CHELLADURAI	38	M	7.2	70	1.58	28	160/90	155	102	160	42	3	YES
3	SMPATH KUMAR	28	M	4.7	58	1.64	21.6	130/80	88	86	164	51	1	NO
4	MOHD.MUTHALIF	60	M	7.8	80	1.66	29	170/110	184	104	180	44	4	YES
5	PONNUSAMY	54	M	5.1	52	1.62	19.8	120/70	140	84	140	56	1	NO
6	RANGANATHAN	40	M	8.2	84	1.68	29.8	160/100	234	106	182	40	4	YES
7	VELUSAMY	62	M	7.4	72	1.74	23.8	164/90	94	88	176	38	3	YES
8	MOORTHY	41	M	4.4	60	1.6	23.43	120/70	112	84	126	48	1	NO
9	KARUPPANNAN	68	M	5.5	60	1.55	24.9	110/70	84	92	168	44	1	NO
10	SATHISH	22	M	7.8	94	1.76	29.3	124/80	98	110	170	34	3	YES
11	MANIVANNAN	44	M	4.2	64	1.7	22.14	140/90	88	82	144	58	1	NO
12	KALAISELVAN	34	M	4.4	58	1.6	22.6	110/80	140	84	140	52	1	NO
13	NANJUNDAN	40	M	6.4	74	1.62	28	150/100	80	92	160	46	3	YES
14	BALASENTHIL	32	M	5.5	70	1.68	24.8	140/90	74	86	146	36	2	NO
15	MAHESWARAN	36	M	4.8	62	1.64	23	120/80	81	88	188	44	1	NO
16	MURUGESAN	40	M	8.8	80	1.64	29.7	160/110	224	94	178	33	5	YES
17	CHANDRKUMAR	39	M	4.1	68	1.68	24	110/70	86	78	165	55	1	NO
18	KRISHNASAMY	52	M	5.5	62	1.58	24.8	140/80	146	86	146	36	2	NO
19	ARUMUGAM	70	M	6	70	1.62	26.67	150/100	94	84	170	48	2	NO
20	KUMARASAMY	48	M	6.7	80	1.66	29	140/90	174	96	146	50	3	YES
21	JEBARAJ	42	M	7.4	84	1.76	27.11	160/100	146	106	188	52	4	YES
22	KALIAPPAN	58	M	5.5	58	1.64	21.56	110/80	142	78	124	56	1	NO
23	MADASAMY	66	M	4.4	55	1.63	20.7	120/80	84	80	155	46	1	NO
24	VIJAYKUMAR	41	M	7	71	1.77	22.66	150/90	106	84	166	56	3	YES

25	SUBBURAJ	37	M	5.8	64	1.66	23.22	160/90	90	92	146	48	2	NO
26	KARTHIK	24	M	4.1	56	1.66	20.32	124/80	88	84	156	45	1	NO
27	PALANISAMY	56	M	5.2	71	1.67	25.46	150/100	84	89	144	55	2	NO
28	VAIKUNTA RAMAN	62	M	7.2	70	1.6	27.34	160/100	166	94	164	55	3	YES
29	JUSTIN PRASAD	37	M	5.2	68	1.68	24	140/90	98	92	144	38	2	NO
30	JAYARAJ	44	M	5.8	70	1.64	26	150/100	86	98	166	48	2	YES
31	SHANMUGAM	60	M	6.1	58	1.56	23.83	120/80	212	84	182	50	2	NO
32	LIYAKATHALI	59	M	4.4	55	1.64	20.44	130/70	87	84	202	56	1	NO
33	MUNIYAPPAN	66	M	5.4	64	1.62	24.38	150/90	138	88	146	48	2	NO
34	ALAGESAN	45	M	7.8	80	1.69	28	140/90	98	104	172	35	4	YES
35	RAVIKUMR	33	M	5.2	74	1.66	26.85	124/80	74	89	144	38	1	NO
36	KUMARESAN	40	M	6.4	78	1.7	26	160/100	87	90	176	34	3	YES
37	MUTHUSAMY	45	M	6.8	72	1.58	28.84	120/80	78	102	156	22	3	YES
38	KALANIDHI	42	M	4.4	60	1.64	22.3	130/70	94	84	124	55	1	NO
39	SARAVANAN	33	M	3.8	64	1.67	22.94	120/80	76	86	144	32	1	NO
40	SIVAPRAKASH	48	M	7.8	80	1.62	30.48	160/100	83	107	180	44	3	NO
41	GANESAN	52	M	7.4	67	1.68	23.73	170/110	184	88	142	38	3	YES
42	SUNDAR RAJ	58	M	7.8	80	1.6	31.25	190/110	110	98	190	36	5	YES
43	RAJASEKAR	38	M	5.2	56	1.64	20.82	140/90	88	84	164	55	2	NO
44	SURESH	28	M	4.1	60	1.68	21.25	120/70	87	87	166	42	1	NO
45	GOVINDARAJ	33	M	6.4	68	1.62	25.91	150/100	120	89	188	46	3	YES
46	GIRINIVASAN	42	M	4.4	58	1.66	21	110/70	78	84	166	48	1	NO
47	KANNADASAN	46	M	5.8	74	1.72	25	140/90	102	88	148	42	2	NO
48	KARUPPASAMY	64	M	6.7	62	1.6	24.21	170/100	145	86	184	34	4	YES
49	PALANIAPPAN	41	M	5.5	64	1.66	23.22	160/90	77	89	144	38	2	NO
50	FATHIMA	64	F	8.1	82	1.68	29	180/110	224	108	206	33	5	YES
51	KUPPUTHAI	58	F	6.8	55	1.46	25.8	130/80	146	90	188	44	4	YES
52	DHANAM	55	F	5.6	56	1.52	24.23	124/80	112	78	156	60	2	NO

53	PALANIAMMAL	60	F	4.4	52	1.56	21.36	130/80	148	76	148	56	1	NO
54	SELVI	45	F	4.2	55	1.58	22	110/70	88	84	144	40	2	NO
55	MAHALKSHMI	38	F	5.6	64	1.55	26.63	120/70	74	94	144	48	2	NO
56	MARAL	57	F	7.4	52	1.6	20.31	140/90	260	78	188	44	4	YES
57	SUPPULAKSHMI	56	F	6.8	60	1.54	25.3	130/80	142	88	156	52	3	YES
58	MANIMEGALAI	40	F	5.8	68	1.61	26.23	110/80	92	94	146	38	2	NO
59	KAMALAM	52	F	5.6	55	1.46	26.9	120/80	88	94	133	52	2	YES
60	KAMATCHI	51	F	7.1	68	1.55	28.3	170/100	212	98	94	24	4	YES
61	STELLA	36	F	4.4	70	1.68	24.8	110/70	84	102	114	35	2	NO
62	RAMUTHAI	60	F	6.3	45	1.56	18.5	150/100	78	74	84	38	2	NO
63	CHELLAMMAL	56	F	6.2	64	1.58	25.63	150/90	162	76	144	41	3	YES
64	JEBAMARY	40	F	6.8	84	1.61	32.4	120/80	88	112	160	52	2	NO
65	CHITHIRASELVI	34	F	6.6	78	1.56	32	110/80	94	106	160	44	2	YES
66	ARULMARY	44	F	4.2	55	1.6	21.48	140/90	98	80	93	33	2	NO
67	SARASWATHI	51	F	6.8	60	1.58	24	150/100	156	84	134	56	3	YES
68	FATHIMA	55	F	8.1	84	1.56	34.51	170/110	180	114	224	28	5	YES
69	SAMPOORNAM	70	F	6.8	55	1.55	22.89	170/100	112	74	166	60	3	YES
70	RANI	46	F	4.4	50	1.6	19.53	110/70	76	76	71	36	1	NO
71	AMMLAMMAL	67	F	5.9	56	1.48	25.56	130/70	186	84	88	44	3	NO
72	BAGAVATHY	54	F	5	44	1.58	17.62	140/90	84	75	166	54	2	NO
73	MARATHAL	52	F	6.6	60	1.52	25.96	160/90	178	84	122	36	4	YES
74	PATTAL	58	F	5.2	51	1.56	20.95	110/70	146	77	80	55	2	NO
75	MAHESWARI	34	F	5.1	60	1.68	21.25	130/70	76	96	112	24	2	NO
76	VALARMATHI	48	F	5.8	55	1.58	22	120/70	166	88	146	48	3	YES
77	AMUTHAVALLI	55	F	6.6	78	1.62	29.72	170/100	98	104	136	38	3	YES
78	PALANATHAL	59	F	7.6	64	24	25	180/110	270	78	186	28	4	YES
79	KANAGAVENI	44	F	3.8	48	1.52	20.77	120/74	87	78	144	36	1	NO
80	GANDHIMATHI	48	F	4.6	66	1.64	24.5	110/70	96	94	160	54	2	NO
81	POOVATHAL	62	F	7.2	58	1.52	25.1	162/100	194	90	144	33	4	YES

82	EZHILARASI	45	F	4.4	52	1.44	25	110/70	68	88	136	55	1	NO
83	SENKAMALAM	55	F	5.8	62	1.55	25.8	150/90	96	88	147	32	3	YES
84	SARADA	60	F	7.6	66	1.57	26.77	180/100	222	80	180	38	4	YES
85	POONGODI	42	F	5.1	60	1.66	21.77	124/70	83	76	144	46	1	NO
86	RASATHI	39	F	4.8	60	1.55	24.97	110/60	78	80	111	35	1	NO
87	PUNITHAVATHI	46	F	3.8	54	1.64	20	120/60	88	74	140	42	1	NO
88	SUJATHA	58	F	7	56	1.5	24.88	170/90	166	78	180	41	4	YES
89	SUPPAL	66	F	6.8	44	1.48	20	160/86	88	76	166	38	3	YES
90	MARATHAL	64	F	5.9	58	1.6	22.65	130/70	180	74	144	36	2	NO
91	PALANIYAMMAL	59	F	6.1	55	1.5	24.44	120/70	168	78	166	52	2	NO
92	THAMILARASI	50	F	6.4	54	1.44	26	160/100	112	80	184	40	4	YES
93	PARIPOORANAM	56	F	5.1	60	1.7	20.76	110/80	146	84	145	52	2	NO
94	BOOMATHI	48	F	6.6	50	1.44	24.11	120/70	124	80	160	35	3	YES
95	MANJULA	42	F	4.2	56	1.6	21.87	110/70	88	78	156	44	2	NO
96	ALAMELAMMAL	48	F	4.8	61	1.56	25	140/86	88	76	144	48	2	NO
97	MUNEESWARI	47	F	6.1	58	1.58	23.23	130/80	140	74	160	44	3	YES
98	KALIYAMMAL	54	F	7.7	64	1.5	28.44	160/100	184	88	184	55	4	YES
99	BAGYA	55	F	6.4	61	1.58	24.43	140/100	84	78	160	41	3	YES
100	JOTHIMANI	55	F	5.4	48	1.54	20.23	160/90	182	76	148	51	2	No